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Archives of Internal Medicine

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PEPTIC ULCER

THE EFFECT OF PARENTERAL INJECTIONS OF PURIFIED MILK PROTEINS ON THE SYMPTOMS AND PROGRESS *

LAY MARTIN, M.D.

BALTIMORE

This paper appears only as a preliminary report. The results of the study have been so interesting and some of them so conclusive that I could not resist presenting the matter at the present time.

By peptic ulcers I mean those on both sides of the pylorus.

As far as I can discover, the first voluntary administrator of foreign protein in the treatment for peptic ulcer was Gottfried Holler,[1] who reported on the matter in 1921.

In 1922, Pribram,[2] a surgeon in Bier's Clinic, published his reports on the treatment for peptic ulcers with a crystallized vegetable protein.[3] His dosage was gradually increased from 0.2 to 1 cc. His results were more or less similar to those of Holler. Both concluded that this form of treatment was a valuable adjunct to the armamentarium and in many ways was much more reliable than the classic medical treatment of the day. They differed somewhat in their method of administering the drug; Holler placed his patients in bed, while Pribram asserted that one of the most marked advantages lay in the economic side, i.e., the treatment could be given to ambulatory patients in such a manner that they did not lose time from work. At that time, such a condition was important in Germany.

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* Submitted for publication, Oct. 13, 1928.

* Address delivered before the American Gastro-Enterological Association, April 30, 1928.

* From the Gastro-Intestinal Clinic of the Johns Hopkins University School of Medicine.

1. Holler: Ist eine Organische Vaguserkrankung die Ursache des Ulcus Ventriculi Chronicum beim Menschen? Die Grundlage zu eines neuen Therapie des Ulcus Ventriculi und Duodeni, Wien. klin. Wchnschr. **34**:223, 1921.

2. Pribram: Parenteral Reizbehandlung des Magen- und Duodenal-geschwüre, Med. Klin. **18**:958, 1922; Proteintherapie und chirurgische Therapie des Magengeschwüre, Klin. Wchnschr. **2**:2112, 1923; Proteintherapie und chirurgische Therapie des Magen- und Duodenalgeschwüre, Deutsche med. Wchnschr. **51**:141, 1925.

3. The crystallized vegetable protein used was novoprotin.

During the next few years, a considerable number of articles dealing with the problem appeared in Germany. Von Friedrich [4] used various types of protein and came to the conclusion that the crystallized vegetable protein was the best. His results were much less satisfactory than those of Holler and Pribram. Perutz [5] saw good results in postoperative recurrences of ulcers.

Although von Hertlein [6] saw decided benefit, he did not believe that the ultimate results were better than those of the old method. Baake,[7] however, was quite enthusiastic. Kalk [8] had excellent results in about 60 per cent of his cases. In a rather large series—most of which gave indisputable x-ray evidence of ulcer—Grote and Bergman [9] found that 69 per cent of their patients were greatly helped or cured. Hampfel [10] used the method frequently with good results.

All observers agree that the first result of the injection was disappearance of pain; in a great many cases, this is followed by a gradual cessation of other symptoms until frequently all symptoms have disappeared. This has usually happened by the third or fourth injection. Most of the physicians prefer to give the material intravenously, and practically all agree that a slight degree of reaction is necessary, their feeling being that there is direct improvement in proportion to the amount of reaction —recognizing that this must, of course, be kept within fairly restricted limits. Holler thought that without a fairly severe reaction results are not to be expected. Pribram was much more conservative and with Baake, Perutz and Kalk, thought that the reaction should be kept at a minimum, this minimum being distinctly necessary. Von Friedrich did not see any relation between the degree of reaction and improvement.

The vaccineurine which was at first used by Holler, Perutz and von Friedrich and which was made from *Staphylococcus aureus* and *Bacillus prodigiosus* was discontinued on account of the severity of the reaction. Practically all of the physicians previously mentioned as well as several others relied entirely on the crystallized vegetable protein

4. Von Friedrich: Proteintherapie der peptischen Geschwüre, Arch. f. Verdauungskr. **24**:75, 1925; Zur Frage der Proteinkörpertherapie des Magen- und Duodenal-geschwüre, München. med. Wchnschr. **11**:428, 1925.

5. Perutz: Parenteral Eiweisstherapie beim Ulcus Ventriculi, München. med Wchnschr. **52**:1527, 1923.

6. Von Hertlein: Ueber die Anwendung des Novoprotins beim Ulcus Ventriculi und Duodeni, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **35**:15, 1925.

7. Baake: Die Proteinkörpertherapie beim Magen- und Duodenal-ukus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:404, 1925.

8. Kalk: Erfahrungen mit Proteinkörpertherapie des Ulcus Duodeni und Ventriculi, Klin. Wchnschr. **28**:1310, 1923.

9. Grote and Bergman: Ueber Novoprotin Behandlung des Magengeschwüre, Zentralbl. f. inn. Med. **45**:337, 1924.

10. Hampfel: Die Proteinkörpertherapie mit Novoprotin, speziell beim Ulcus Ventriculi noch Pribram, Med. Klin. **26**:901, 1923.

given intravenously. Later, Ceranke [11] reported good results with the use of a casein preparation.

A comparison of the accumulated reports of many writers reveals the following rather interesting observations: (*a*) In the majority of cases, there is a slight fall in gastric acidity at the end of treatment. A repetition of the gastric analyses in these cases at a later date showed that the acidity was within normal limits. In a fair proportion of the cases there was no change, and in a few there was a rise in the gastric acidity. (*b*) The roentgen-ray examinations in these same cases show varying results. Ceranke reported disappearance of the shadow defect in 25 per cent of his cases, Kalk in 8 per cent and Pribram in 7 per cent. They all agreed that frequently the amount of spasm is markedly diminished or the tonicity becomes normal.

Hampfel, von Gromer,[12] Berger,[13] and Pribram were all particularly enthusiastic in the use of the crystallized vegetable protein in cases in which medical treatment has been tried for a considerable time without avail. Pribram particularly advised using it when pyloric obstruction appeared to be present. Under the influence of the protein this obstruction disappeared and would seem, therefore, to have been due to spasm.

Pribram advised giving the crystallized vegetable protein in a course of ten injections, at intervals of from two to four days. At the end of this time, if symptoms still persisted, he gave another course. In an article appearing in 1925, he came to the conclusion that any patient going through three cases of treatment without improvement should be operated on.

The new method has naturally been opposed. In making histologic studies on patients coming to operation Marx [14] could not find any signs of healing in those who had been treated. To meet the rather sensible objection of the protagonists that this was to be expected since only the patients whose treatment had been unsuccessful came to operation, Gohrbrandt [15] told of some of his operative and histologic experiences. He did not believe that any conclusion can be drawn from macroscopic examination of ulcer tissue. For various reasons which were not connected with the symptoms of ulcer, he operated on several patients who

11. Ceranke: Ueber den Erfolg der Reizkörpertherapie bei Ulcus Ventriculi und Duodeni, Wein. Arch. f. inn. Med. **13**:391, 1927.

12. Von Gromer: Die therapeutische Wirkung des Novoprotin bei Ulcus Ventriculi, Med. Klin. **22**:991, 1926.

13. Berger: Ueber Novoprotin Behandlung des Ulcus Ventriculi und Duodeni, München. med. Wchnschr. **27**:924, 1924.

14. Marx: Zur Wirkung der Proteinkörpertherapie auf das anatomische Bild des Ulcus Ventriculi und Duodeni, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:447, 1925.

15. Gohrbrandt: Zum anatomischen Bilde der mit Novoprotin behandelten Magen- und Darm-geschwüre, Klin. Wchnschr. **4**:2492, 1925.

had undergone treatment and were symptom-free. In a series of seven patients not only did he find the ulcers still present, but in some of them there was no granulation tissue.

METHOD OF EXPERIMENT

Twenty-four patients with the history, signs and symptoms and the roentgenographic and laboratory evidence of peptic ulcer were given intramuscular injections of milk protein. These patients were chosen because the evidence from all sides concurred in the diagnosis. Other than choosing properly diagnosed cases I have not attempted any other form of selection.

Observations extended over a period of eighteen months, but as my interest has increased with time the majority fall within the past six months.

Twenty-three men (two of them colored) and one colored woman were treated. Their ages were between 24 and 65. Other than peptic ulcer the only complications of interest were psoriasis in one patient, bronchiectasis in one and arthritis in two.

A nonspecific milk preparation[16] was used.

All patients received the milk preparation deep in the buttocks. Care must be taken that one is not making the injection into a deep vein; I have encountered this circumstance twice. Injections have been given at irregular intervals. The first patients received from one to three injections at weekly intervals; the later ones received from one to seven injections at two to three day intervals. The dosage was always at 10 cc.

Control roentgenograms were always made, after which the patients were given their first dose of the nonspecific milk preparation. Twenty minutes later, they were given a second glass of barium sulphate, and another series of films were taken. Films were made at five minute intervals. Gastric analyses were done just prior to the control films. The Ewald test meal was used, and the stomach content was removed one hour after ingestion.

Some of the patients were placed on a soft diet for a week; in a few this was done because they had been on such a diet for months. Others were allowed to eat what they wanted.

At various times, a second and a third gastric analysis was done; roentgenograms were also repeated.

All the patients were ambulatory, most of them being at work while the course of injections was being given.

OBSERVATIONS

The first change that one notices during the treatment is a marked decrease in pain. This may happen after the first injection, and it is infrequent that the pain does not decrease by the second or third. This is in itself, of course, rather pleasing to the patient. Later on, there is considerable decrease in the other symptoms that accompany the disease. Regurgitation, eructation and gaseous disturbances of the abdomen all disappear in proportion to the general degree of improvement obtained by each individual patient. This may vary considerably.

16. The nonspecific milk preparation used was Aolan. It is distributed in this country by the H. A. Metz Laboratories, Inc., New York, which has been kind enough to keep me supplied to the extent of my needs.

It is not unusual to have the patient state that on the night following the injection he has some increase of pain, particularly pain caused by gas. As the number of injections increases, less and less focal reaction is observed.

Locally, I have seen a reaction in one patient. This appeared following the third injection and was evidenced by fever, local inflammation and tenderness. The fourth injection five days later produced a much smaller reaction. Following his third dose, one patient had a reaction with nausea, vomiting and chill followed by sweating. In another patient this followed the fourth injection.

The results of the treatment on the gastric secretion in twenty-one patients are shown in table 1. The immediate and late effects were decidedly different. In the first group there was an increase of gastric acidity in five of the seventeen cases, an approximate constancy in nine, and a true decrease in three.

Of these twenty-one cases, eight were observed after a period of from four to eighteen months. In this group there was an increase of acid in two, an approximate constancy in two and a true decrease in four.

The roentgen-ray observations are equally interesting. In fourteen instances films were made from twenty to thirty minutes after the injection of a nonspecific milk preparation. It was not possible in any case to be sure that there was definite relaxation of the muscular tone of the stomach within thirty minutes after the primary injection. This came rather as a surprise, for in light of the excellent work of Müller and Petersen [17] on the effect of injections of foreign protein I was hopeful of obtaining visible evidence of this occurrence. They showed kymographic tracings of contraction of the stomach before and after the injection of the nonspecific milk preparation. The tracings were obtained by inflating a small balloon which the patient had swallowed. This was distended by air and attached to a manometer which recorded the contractions of the muscles of the stomach on a drum. This may be seen in figure 1.

In eighteen instances, films were taken just after the completion of treatment. In one case only was there a disappearance of the shadow defect (figs. 2 and 3). In three cases there appeared to be either greater definiteness of the defect or more spasm. In six cases either a smaller defect or markedly less spasm or both were present (figs. 4, 5, 6 and 7). In the nine remaining cases, a definite change could not be determined in the x-ray films made at the end of treatment.

As many as eight patients were reexamined from four to eight months after treatment. When this paper was written, five of them showed a smaller defect or less spasm or both. The other three did not show any change.

17. Müller and Petersen: Ueber die Wirkung der Proteinkörperinjection auf den Magen-innervation, München. med. Wchnschr. **74**:531 and 588, 1927.

TABLE 1.—*Summary of Treatment, Laboratory Investigations and Results on Twenty-Four Patients Following Parenteral Injection of Nonspecific Milk Preparation*

Case	No. of Injections	Interval in Days	Changes in Gastric Acidity: Control	Changes in Gastric Acidity: End of Treatment	Changes in Gastric Acidity: From 4 to 18 Months Later	Time Since Last Treatment	Condition of Patient	Changes in Roentgenograms: Control	Changes in Roentgenograms: ½ Hour after Injection	Changes in Roentgenograms: End of Treatment	Changes in Roentgenograms: From 2 to 18 Months Treatment
1	6	7	20-36	.....	75-109	Operation	At operation, two healed ulcers, many adhesions	Irritable stomach, defect due to adhesions?	.....	No change	No change
2	6	7	26-72	30-70	.....	1 month	Clinically well	Irritable stomach, filling defect in duodenum	.....	Normal stomach and duodenum	
3	12	3-7	60-76	50-70	.....	2 months	Clinically well	Atonic dilated stomach, large duodenal defect, partial obstruction	No change	Good tone, cap almost smooth	
4	10	3-5	0-14	34-60	.....	2 months	Improved	Gastric ulcer niche and hourglass contraction	No change	Less spasm opposite ulcer niche which is smaller	
5	7	3	68-92	32-42	40-62	Operation	At operation, duodenal ulcer	Irritable stomach, defect in pylorus due to spasm?	.....	No change	
6	6	3-6	32-62	48-66	.....	2 months	Clinically well	Irritable spastic stomach, defect in duodenum	No change	More spasm and greater defect	Less spasm and defect
7	12	2-4	62-94	74-88	.....	3 months	Clinically well	Large spastic stomach, large defects in duodenum and pylorus	No change	No change	No change
8	5	3-4	40-52	.....	.....	1 month	Clinically well	Irritable stomach, filling defect in cap due to ulcer			
9	13	3-7	40-72	42-62	.....	Weekly injections	Improved	Irregularity at duodenum due to operative procedure	No change	Less spasm of stomach	
10	3	5-6	64-90	.....	56-80	15 months	Clinically well	Irritable stomach, filling defect in pylorus	No change	No change	Normal tone, defect same
11	9	5-9	52-68	60-100	72-92	3 months, treatment at intervals	Worse	Large ulceration of pylorus and duodenum	No change	Greater spasm, defect same	

12	8	2-3	60-84	80-110	.....	1 month	Clinically well	Hyperactive stomach, filling defect in duodenum	No change	No change	
13	7	3-4	58-72	60-90	.....	2 months	Clinically well	Duodenal ulcer	.....	More spasm of stomach, defect more pronounced	
14	2	7	72-94	.....	58-96	18 months	Clinically well	Very irritable stomach, defect in duodenum	No change	.....	Normal tone, filling defect same
15	2	7	74-92	60-70	30-46	6 months	Clinically well	Irritable dilated stomach, large defect in duodenum	No change	No change	No change
16	6	4	40-56	60-88	.....	Operation	At operation, duodenal ulcer	Large defect in duodenum	No change	No change	
17	6	3-4	40-75	10-30	20-52	3 months	Clinically well	Large atonic stomach, large defect in pylorus and duodenum, partial obstruction	No change	No change	Outline of duodenum seen, no change in atonicity
18	3	5-6	90-112	.....	.....	12 months	Clinically well	Irritable stomach, defect in duodenum	No change		
19	3	7	.....	.....	.....	14 months	Clinically well	Defect in pylorus, markedly irritable stomach			
20	7	3-6	58-76	30-70	.....	2 months	Clinically well	Large filling defect in duodenum, very irritable stomach	No change	No change	
21	3	5-6	50-70	.....	12-64	14 months	Clinically well	Large filling defect in duodenum	.....	.....	Less spasm and defect
22	4	3-5	42-62	46-64	.....	2 months	Clinically well	Atonic stomach, filling defect in duodenum, partial obstruction	.....	Normal stomach, filling defect in duodenum	
23	4	4-5	30-48	34-52	.....	2 months	Clinically well	Irritable spastic stomach, filling defect in duodenum	.....	Normal tone defect same	
24	5	3-4	84-96	.....	.....	2 months	Improved	Very spastic stomach, duodenal ulcer			

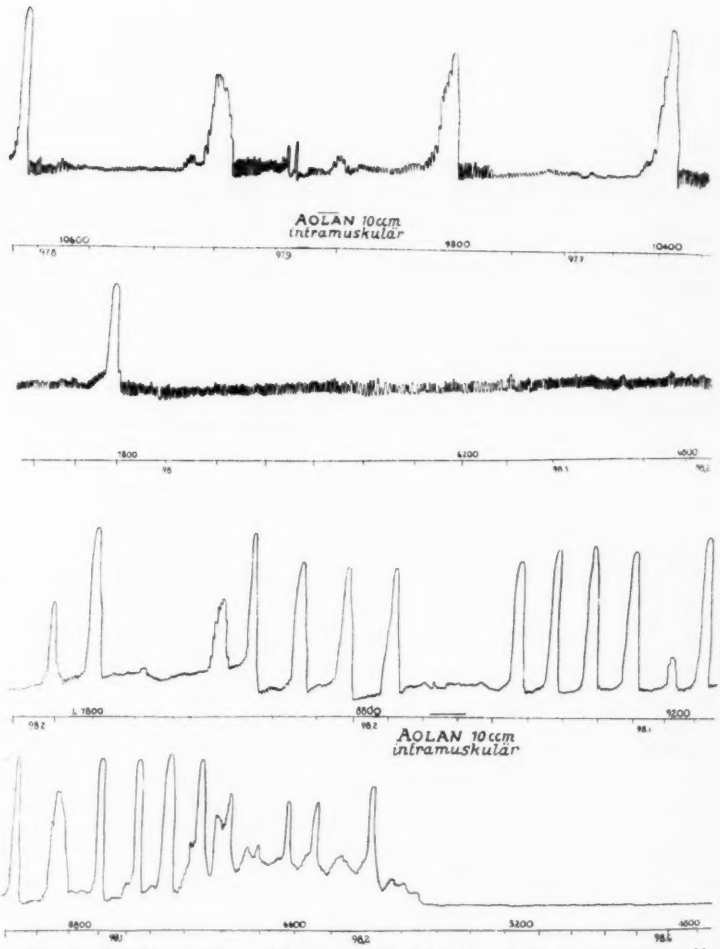

Fig. 1.—Inhibitory effect of intramuscular injection of 10 cc. of a nonspecific milk preparation on gastric contraction in two patients. Taken from Müller and Petersen.

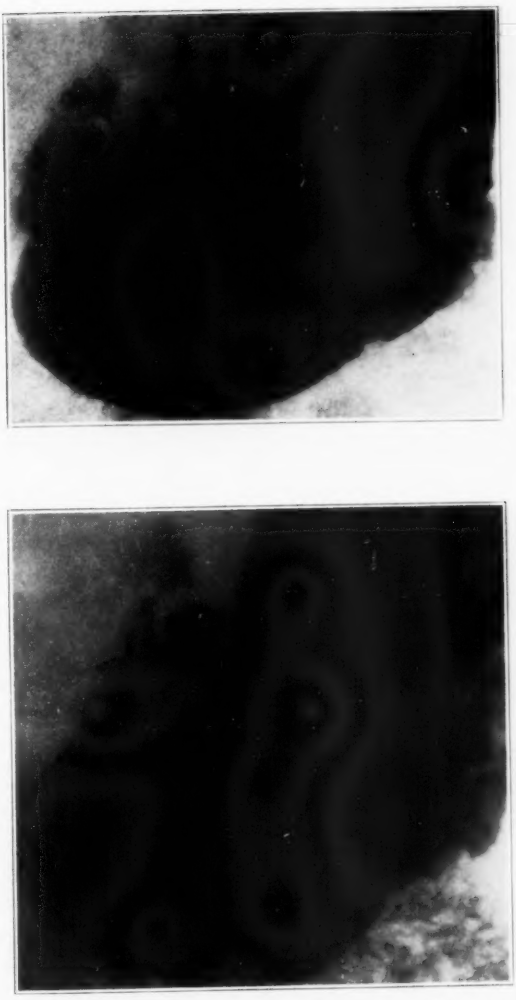

Fig. 2 (case 2).—Duodenal ulcer in control.

Examinations of the stools for the presence of occult blood were made on all except two patients. The benzidine slide method was used. Twelve were found to give positive tests. This did not persist long in any instance.

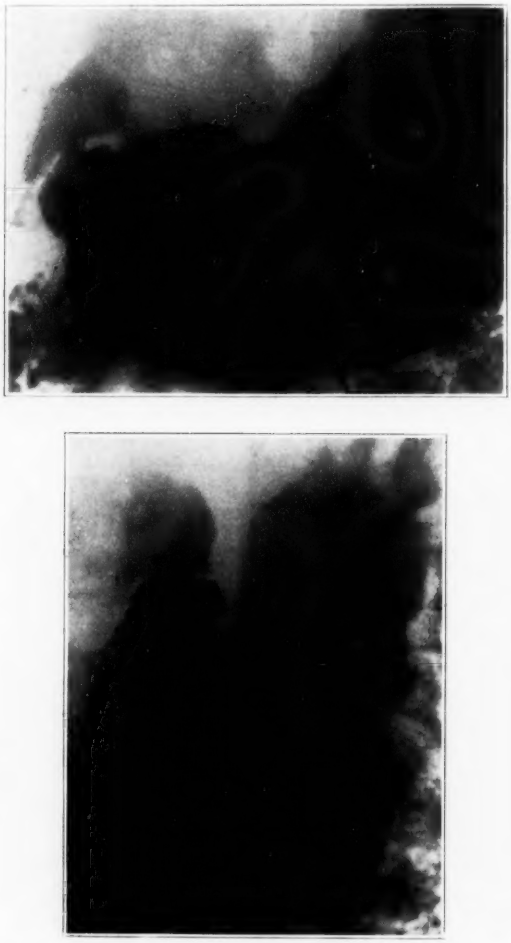

Fig. 3 (case 2).—Normal stomach and duodenum at end of treatment.

It is not a rare occurrence to have patients complain of constipation while they are taking the course of treatment. A control film and one taken during treatment in case 17 may demonstrate the cause (figs. 8 to 10).

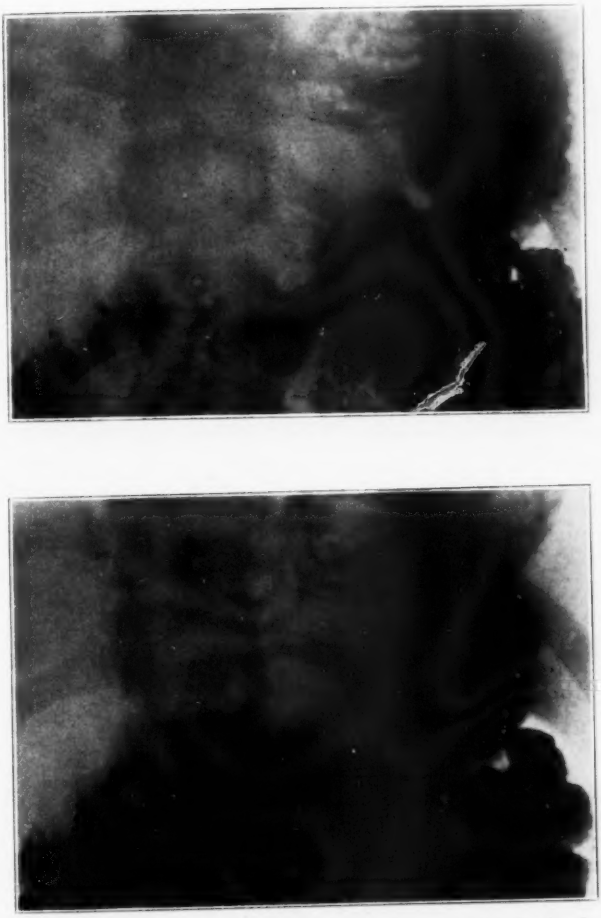

Fig. 4 (case 14).—Tremendous irritability and spasm and duodenal ulcer in control.

Before I consider the clinical results in these twenty-four patients, it may be wise to divide them into two classes, namely, those with acute and those with chronic cases. In the first class are included all those patients who were having their first attack or their second or third after a period of well-being lasting more than from four to six months. In the second class are placed those who have had symptoms at varying intervals for years, those who are fairly comfortable while receiving

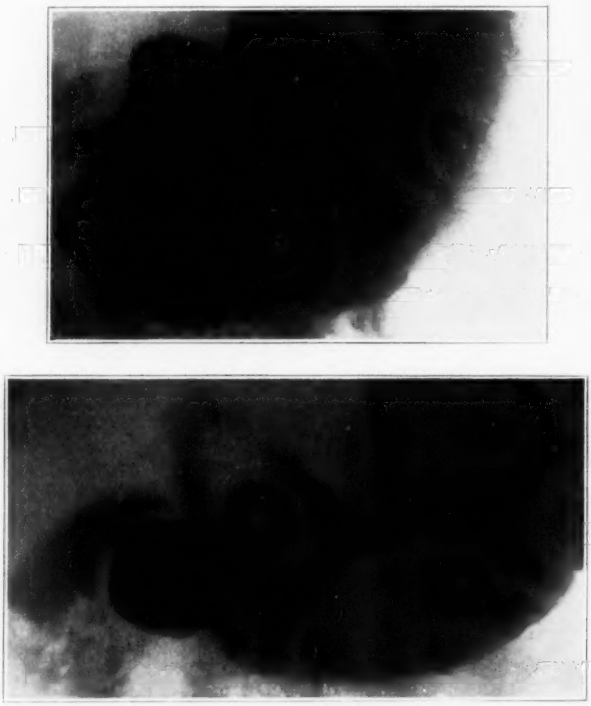

Fig. 5 (case 14).—Eighteen months after treatment, showing good tone and duodenal defect.

treatment but who have a relapse when treatment is stopped and those who have had many acute attacks and are now suffering constant discomfort. Fifteen patients were considered to be suffering from acute ulcers and nine from chronic ulcers. Twelve of the former are entirely without symptoms; two are decidedly better and one is worse. Among the nine patients with chronic ulcers, five are without symptoms, although two of them had partial pyloric obstructions, one is much better and three were operated on for relief from symptoms.

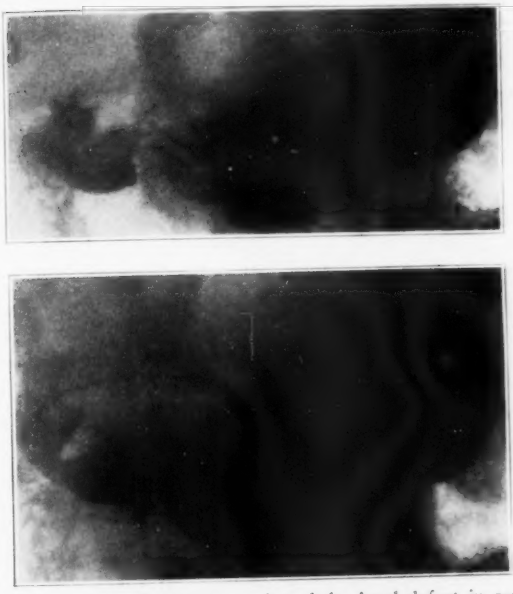

Fig. 6 (case 10).—Spastic stomach and duodenal defect in control.

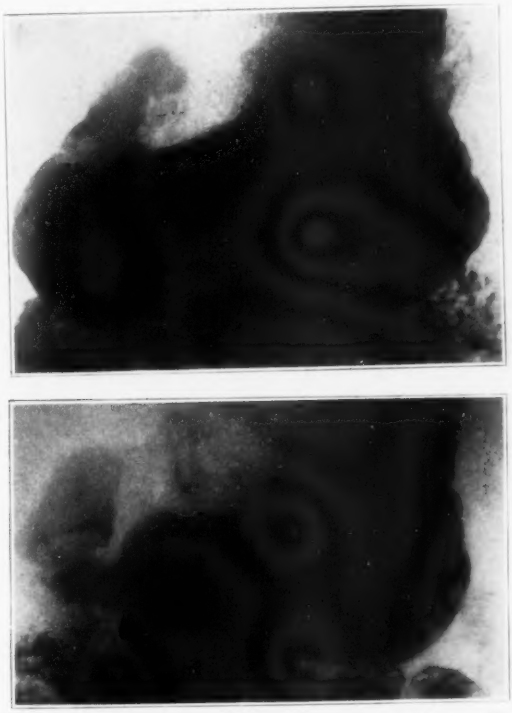

Fig. 7 (case 10).—Sixteen months after treatment, showing smaller defect and perhaps less spasm.

If this is placed on a percentage basis, 80 per cent of the patients with acute forms of the disease are symptom-free. If one includes with them the same type of chronic case, one finds that 66.6 per cent of all patients have been clinically cured. The percentage of cure or betterment in both groups is 83.2. It is also necessary to bear in mind that after the first week almost all these patients ate all manner of food.

Only three patients came to operation; two of them showed ulcers on the anterior surface that were not remarkable. The third case showed marked adhesions about the duodenum and gallbladder without constriction of the pylorus; there were two healed ulcers in the duodenum. Gastro-enterostomies were done on all these patients; so sections could not be made (table 2).

COMMENT

There is no doubt that one may obtain remarkable results in the treatment of these patients by the intramuscular injection of milk pro-

TABLE 2.—*Clinical Results on Twenty-Four Patients*

	Well	Improved	Per Cent Combined	Worse	Operated On	
					Number	Per Cent
Acute	12	2	93.3	1	0	00.0
Chronic	5	1	66.6	0	3	33.3
Total	17	3	83.2	1	3	16.8

tein. This fact in itself, although interesting, is not of great therapeutic value unless the improvement so obtained is stable. As already noted, twelve of the fifteen patients with acute forms are entirely without symptoms and have been so for from two to fifteen months. Only five of them have been under observation for more than a year; they are all clinically well. The remainder have been symptom-free for from three to ten months. It is also important to note that these patients have been on a full diet. Two patients with acute forms of the disease have been improved and have preferred to remain in this state rather than be operated on. One has become decidedly worse after a temporary improvement and will, in my judgment, come to operation.

Among the chronic cases there have been some startling results. One patient has been well for eighteen months. He received only two injections of the nonspecific milk preparation, and as he was the first patient treated, the injections were given a week apart. In spite of this remarkable result, if he came to me today for the first time he would receive from five to seven injections at intervals of from two to three days. The latter method of timing gives good results, but it too may be changed later. The patient in case 15, whose recovery was the most remarkable of all, had been sick for twenty years. For six months, he had been

in constant pain and discomfort. Four days after the initial injection, he was practically without pain. He received one more injection and was allowed to go home. He reported after a period of six months that he had been entirely well except for an occasional mild attack of gas disturbance. The other three patients who are now clinically well had all suffered for years. One of them had had a gastro-enterostomy done

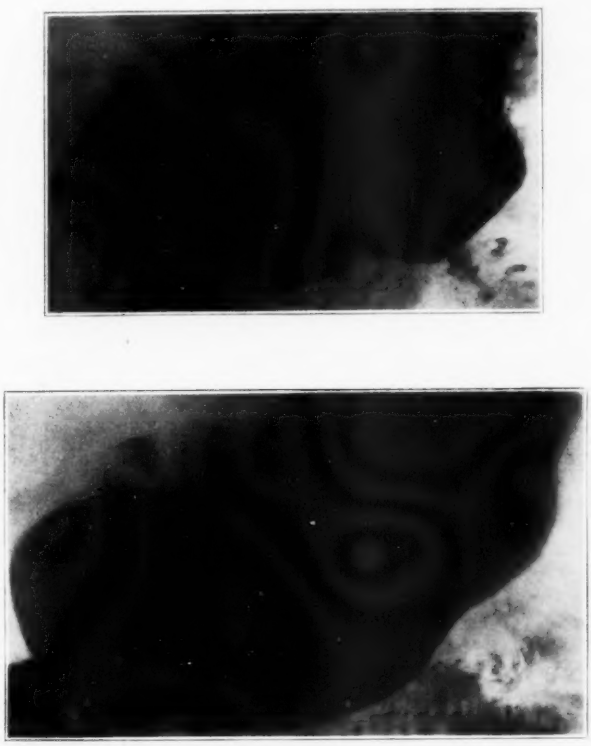

Fig. 8 (case 17).—Duodenal ulcer with marked six hour retention in control.

five years before I saw him; since then he had had many recurrences and had been miserable for six months, just prior to treatment with the nonspecific milk preparation. His pain disappeared after three injections, and for the next three weeks he was without symptoms. They suddenly reappeared in great intensity, but were controlled by a second series of injections. At the time this paper was written, he had been well for two months.

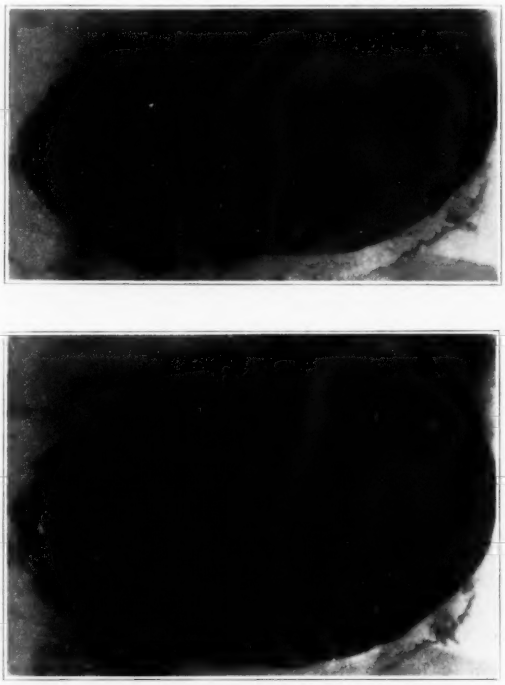

Fig. 9 (case 17).—Appearance during treatment. Complaint, constipation. Spastic small intestine.

Fig. 10 (case 17).—End of treatment. Hazy outline of cap.

Case 1 offers an interesting study. The patient had had many recurrences in the past four or five years. In spite of medical treatment his condition had been getting gradually worse for the past year or so, and during the month before the first injection was made his condition was one of great discomfort. He received three injections before his pain left, and he remained markedly improved for six months although he had moderate discomfort from gas. One month before admission his pain returned, and it could not be controlled by the nonspecific milk preparation. At operation, two healed ulcers and many adhesions were found. There was no obstruction.

Cases 16 and 5 are still a mystery to me, for it would seem that the same good results should have been obtained in them as in the others. The former did not show the slightest improvement. At operation, a

TABLE 3.—*Individual Chart*

Case 15									
Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X-Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
Jan. 18	+	0	0	74 & 92	Ulcer of pyloric duodenal region	Regular	+ + +	+ + +	—
Jan. 20	—	0	—	—	—	—	+	+	Feels better
Jan. 25	+	0	0	—	—	—	0	0	No symptoms
March 1	—	0	—	—	—	—	0	0	No symptoms
April 23	—	0	0	60 & 76	No change	—	0	0	No symptoms; has gained 10 pounds (4.5 Kg.)
June 13	—	0	—	30 & 46	No change	—	0	0	No symptoms; has gained 4 pounds (1.8 Kg.) more

fairly large ulcer was found. There was no obstruction. The patient in case 5 did exceptionally well after one injection. He had been on good medical treatment for months, and the pain which had been present for three months and which could be relieved only by codeine sulphate disappeared in twelve hours after one injection. He was so completely without symptoms that he did not receive any more of the nonspecific milk preparation. Four months later symptoms returned with all their former intensity. Six injections did not give any relief. At operation, a typical duodenal ulcer was found.

The patient in case 9 had a ruptured duodenal ulcer five years before I saw him. The leak was repaired with a purse-string suture. He had several recurrences and in the last three months did not obtain relief from good medical treatment. After some experimenting it was found that he could be kept practically symptom-free if he received one injection each week or ten days.

Tables 3, 4 and 5 better demonstrate the typical changes observed in some of the patients.

DOSAGE

The question of dosage is far from being settled. As already noted, 10 cc. of a nonspecific milk preparation has been the amount used for each injection. In case 8 a local reaction similar to the Arthus phe-

TABLE 4.—*Individual Chart*

Case 16

Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X-Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
April 2	+	0	0	36 & 56	Ulcer of duodenum	Soft	++	++	—
April 9	+	0	0	—	—	—	+	++	No change
April 16	+	0	—	—	—	—	0	±	Feels much better
April 20	+	0	—	—	—	—	+	+	Complains of much gas
April 24	+	0	—	60 & 88	No change	—	+	+	No improvement
May 1	+	0	—	—	—	—	+	+	No improvement
May 9	—	0	—	—	—	—	+	+	Operation, posterior gastro-enterostomy for the ulcer
June 4	—	0	—	—	—	Regular	0	0	No gastrointestinal symptoms except some gas

TABLE 5.—*Individual Chart*

Case 17

Date	Nonspecific Milk Preparation	Vomiting	Stool	Gastric Analysis	X-Ray	Diet	Pain	Intensity of Symptoms	Course of Symptoms
April 2	—	—	++ blood	40 & 75	Ulcer at pylorus; atonic stomach	Soft	++	++	—
April 4	+	+	++ blood	—	—	Soft	++	++	—
April 9	+	0	+ blood	—	—	Soft	Very little	±	Feels much better
April 13	+	0	0	—	—	Regular	0	0	Feels almost well
April 16	+	0	0	—	—	—	Slight pain ½ hour once	±	
April 19	+	0	0	—	—	—	0	0	Feels like another man
April 27	—	0	0	10 & 30	No change	—	0	0	No symptoms
June 1	—	0	0	—	—	—	Very slight at times	±	Working hard
June 15	—	0	0	20 & 30	Smaller stomach	—	0	0	No symptoms
July 1	—	0	0	—	—	—	—	0	No symptoms

nomenon was produced. The general reactions were probably due more to the presence of a foreign body than to the fact that the patient had been sensitized. In one case the reaction followed the last of these weekly injections (case 18) and in the other, the fourth injection (case 20). The reactions were not nearly so severe as those usually seen after transfusions.

A comparison of the results obtained in relation to the time intervals between injections reveals satisfactory results following any sequence, but work now under way makes me think that shorter and more regular intervals will produce the best and most lasting results.

CONCLUSION

In three cases not included in this series, in which previous gastro-enterostomies or resections had been performed and in which the symptoms of the patients presented a picture much more typical of adhesions than recurrent ulcerations, help was not obtained with a nonspecific milk preparation.

If the cases are followed entirely from the point of view of improvement in laboratory studies, it is true that few changes can be demonstrated. However, when one sees the disappearance of that pinched, haggard look, the resumption of an upright carriage, an ability to eat heartily without fear of consequences and the usual gain in weight and when one realizes that numbers of these men had had previous treatments without avail, one cannot help but be impressed with the results of this form of treatment.

Many excellent results are obtained by the classic medical treatment for ulcer, and time alone will show whether the parenteral injection of a foreign protein offers a more permanent cure. Whatever the future may demonstrate, certainly, the effect of the nonspecific milk preparation on pain and its results when other methods have failed will justify its retention in the therapeutic armamentarium.

REPORT OF CASES UP TO JULY 12, 1928

Case 1.—A white man, aged 48, complained of almost constant pain in the upper part of the abdomen which had been present for about six months, was not relieved by ingestion of food and was increasing in its intensity. His first attack, which occurred five years before admission to the hospital, consisted of a gnawing hunger pain which came on two or three hours after meals and which was relieved by food. Up to six months before admission he had many of these attacks, which lasted from four to seven weeks each, and between attacks he did not have any complaints.

Physical examination showed a tired man who had lost weight and looked bad. There was considerable tenderness in the midepigastric area. The gastric analysis was: free acid, 20, and total, 36. Occult blood was not present in the stools. The x-ray films showed a stomach which was tremendously irritable and which had a filling defect in the duodenum. On Nov. 11, 17 and 27, 1927, he was given 10 cc. of a nonspecific milk preparation. There was complete relief from pain, but he still complained of gaseous distention and fulness. These symptoms continued until May, 1928. The gastric acidity was: free, 75, and total, 109; x-ray examination did not show any change except less gastric spasm. At this time pain recurred which was not alleviated by three injections of a nonspecific milk preparation. At operation, two healed ulcers and many adhesions were found. Following a gastro-enterostomy, he obtained complete relief. He was always on a regular diet.

Case 2.—A white man, aged 32, complained of epigastric pain for the first time. For two weeks he had had a gnawing pain in the upper part of the abdomen which was relieved by food and which appeared two or three hours after meals. His appetite was good, and he had not lost weight. On physical examination, nothing of note was determined. The stool gave a faintly positive test for occult blood, and the gastric analysis was 26 and 72. On the x-ray films a filling defect was seen in the duodenum, and the stomach was irritable. He was given 10 cc. of a nonspecific milk preparation on May 1, 7, 15 and 23 and on June 6 and 13. He was kept on a regular diet, and all symptoms disappeared after the second injection. At the end of treatment, the gastric analysis was 30 and 70; the x-ray films were entirely normal. At the time this paper was written, he was clinically well.

Case 3.—A white man, aged 65, had complained of pain in the upper part of the abdomen for the past five months. It had been acute and accompanied with nausea and vomiting for the past three weeks. For fifteen years he had been having recurrences of a gnawing hunger pain in the epigastrium which at first had been relieved by food or soda. During the interval between the attacks, his general health was excellent. In more recent years, each attack left him feeling a bit weaker and more easily upset. The attack which brought him to the clinic was by far the worst, and nausea, vomiting and anorexia occurred for the first time.

On physical examination, the patient appeared tired, worn, bent and old with a haggard, pinched expression. The blood pressure was 100 systolic; 60, diastolic, and he had an occasional extrasystole; he was markedly below weight and complained bitterly of pain when light pressure was made over the epigastrium. The gastric analysis was 60 and 76; examination of the stool showed occult blood. In the x-ray films an atonic stomach with a large filling defect in the duodenum was seen. He was given 10 cc. of a nonspecific milk preparation on April 24, 27 and 30, May 2, 3, 11, 14 and 23 and on June 7, 11, 15 and 18. After four injections, he was symptomless; occult blood was not found in the stools, and he was put on a regular diet. On May 27 the gastric acidity was 50 and 70, and in one x-ray film the entire duodenum was visualized; the tone of the stomach showed great improvement.

On June 7 the symptoms returned but in a much less severe form. After four injections of the nonspecific milk preparation, he was again in excellent condition and remained so until the time this paper was written. He looked like a different person, walked with an upright carriage and was back again at his work.

Case 4.—A man, aged 44, complained of a severe gnawing pain in the pit of his stomach. For six years he had had recurrent attacks of gnawing hunger pain in the epigastrium which at first was relieved by food, but in the attack that had persisted for six months prior to admission food had less and less ability to help, and the pain was present almost constantly. A great deal of gas was present, but in spite of all this his appetite was good, and he had not lost weight.

Physical examination showed nothing of importance except marked spasm and tenderness in the upper part of the abdomen, especially in the midepigastrium. The stool did not show blood, and the gastric analysis did not reveal any free acid but a total acidity of 14. Fluoroscopic examination showed a niche on the lesser curvature and a marked irregularity at the pylorus. On the x-ray films repeated examinations had not shown the niche, as it was presumably a bit on the posterior surface; the films did, however, show the pyloric irregularity. On May 4, 9, 12, 15, 19, 22, 29 and on June 5 and 19, 1928, he was given 10 cc.

of a nonspecific milk preparation, and although his symptoms were not completely cured he was so much better that he would not consider operation. The last gastric analysis was 34 and 60. The fluoroscopic examination of the stomach showed a smaller niche. He was on a soft diet for months.

CASE 5.—A masseur, aged 28, had been having gastric symptoms for about two years. The previous attacks had lasted for from four to six weeks and had been relieved by routine medical treatment. On admission, he complained of epigastric pain which had been present for six months and for which codeine sulphate had been given recently as the only alternative to constant pain. Except for considerable tenderness and spasm in the epigastrium, the physical examination gave negative results. Gastric analysis was 68 and 92, and the stool contained occult blood. X-ray films showed an irritable stomach with a lateral cap, but a definite ulcer was not made out. On Feb. 8, 1928, he was given 10 cc. of a nonspecific milk preparation. Twelve hours subsequently his pain entirely disappeared, and he was without symptoms for four months. During the period of well-being, the stools were normal; the gastric acidity was 32 and 42, and the x-ray films unchanged. On May 12, the symptoms recurred with all their initial intensity. Five injections of the milk preparation were of no help, and he was operated on, May 25. A large, inflamed, indurated ulcer was found, and, owing to the presence of many adhesions from a previous peritonitis, it was necessary to do an anterior gastro-enterostomy. Relief was immediate and absolute.

CASE 6.—A white man, aged 28, complained of an attack typical of many he had had in the past four years which lasted from four to eight weeks with periods of complete relief in the interim. The symptoms were gnawing hunger pains which food relieved for two or three hours and which awakened him at night. There was considerable gaseous distention and acid eructation. His appetite was good, and he had not lost weight. The symptoms which brought him to the dispensary had been present for about two or three weeks and were not showing any signs of abatement.

Physical examination showed nothing of importance except ragged tonsils and a tender area in the midepigastrium. The stool gave a positive test for blood, and the gastric acidity was 32 and 60. The x-ray films showed a filling defect in the duodenum and an irritable stomach. A nonspecific milk preparation in 10 cc. amounts was given April 23, 27, 30 and May 2, 10 and 16, 1928. There was complete relief from symptoms after the fifth injection, and he had remained free from symptoms up to the time this paper was written. At the end of treatment, the gastric analysis was 48 and 66; the stools did not contain blood, and the filling defect in the x-ray films was smaller; gastric spasm had also decreased. He was on a regular diet and, furthermore, on June 15 developed acute gonorrheal urethritis without gastric symptoms.

CASE 7.—This case was extremely interesting and quite instructive. Five years before admission, the patient developed symptoms of duodenal ulcer and, not being helped by medical treatment, was operated on and a duodenal ulcer found. A pyloroplasty gave him relief for a year, but in the past three years he had severe attacks similar to those prior to operation, and blood had been found in the stool. Twice he had been subjected to the so-called Sippy cure. Between attacks he felt well. On admission, he complained of an epigastric pain of five weeks' duration which was not helped by food. He was 44 years old.

On physical examination the man looked cadaverous and was bent over with pain, which he localized in the epigastrium. There was tenderness at this point, and marked muscle spasm was present. The hemoglobin was 74 per cent (Sahli), and the stools contained occult blood. Gastric analysis showed free acid, 62 and

total acid, 94, and on the x-ray films marked irritability of the stomach was seen. He responded slowly to a nonspecific milk preparation which was given in 10 cc. amounts on April 13, 15, 19, 23 and 27, on May 2, 15, 16, 19, 22 and 28 and on June 4, but after the third injection he felt a great deal better and began to walk with an upright carriage. At the completion of the sixth treatment he felt quite well and continued so until May 15, when another course of the milk preparation was necessitated by a return of symptoms. After that, he remained well. Blood reappeared in the stools on the recurrence of symptoms but was not found on discharge. After the second series of injections the free acid was 74 and total acid 88, and the x-ray films were unchanged. He gained 10 pounds (4.5 Kg.), ate a regular diet and felt extremely well. He looked like a different man.

Case 8.—L. W., the only woman in the series, an intelligent negro cook, for five years had had autumnal recurrences of epigastric gnawing pain which were temporarily relieved by food and which usually lasted from four to eight weeks. For several years, she had had a moderate degree of arthritis. On admission she had been having gastric symptoms for six weeks; this was the first attack to occur in the spring.

The physical examination showed a mild arthritis of the knees and some tenderness in the midepigastrium. Gastric analysis was 40 and 52, and the x-ray films showed an irritable stomach and a deformed cap. Blood was not found in the stool. A nonspecific milk preparation in 10 cc. amounts was given on May 9, 12, 15 and 17, 1928. Following the third injection, the patient developed a large local reaction (Arthus' phenomenon); due to a misunderstanding, she received a fourth injection, but fortunately the reaction was much less intense. The gastric symptoms practically cleared up, and the arthritis was entirely relieved.

Case 9.—A man, aged 46, had his first symptoms three years before admission in perforation of a duodenal ulcer; at operation, a simple purse-string suture was made for a closure. He came to the clinic complaining of pain of three weeks' duration in the epigastrium, more intense one or two hours after eating and temporarily relieved by food. Previous to this he had had three similar attacks; he had been admitted to the hospital and had received the Sippy treatment.

On physical examination, the man was underweight and tired and was bent over from pain and an epigastrium which was tender on palpation. The stool contained occult blood, and the gastric analysis was 40 and 72. Without knowledge of the history, Dr. Baetjer interpreted the x-ray films as follows: "Defect in duodenum due to operative interference." The patient was put on a soft diet and given a nonspecific milk preparation, 10 cc. at a time, on March 26 and 28, on April 9, 16, 19 and 25, May 2, 7, 15 and 21 and on June 1. There was some immediate improvement in the first three weeks, and in the next six he was kept fairly comfortable on one injection a week. During the following six weeks he was without symptoms. At the time this paper was written, he was on a soft diet and had gained 8 pounds (3.6 Kg.).

Case 10.—A man, aged 28, came to the clinic complaining of gnawing hunger pains in the epigastrium which came on when the stomach was empty and which were relieved for two or three hours by food. The attack had been active for four weeks and was similar to four previous ones which had occurred during the last three years. His appetite was good, and he had not lost weight although he was a steel roller.

Physical examination gave essentially negative results. The stool contained blood, and the gastric analysis showed free acid, 64 and total, 96. On the x-ray

films a filling defect was found at the pylorus and the stomach was irritable. The patient was given 10 cc. of a nonspecific milk preparation on March 31 and on April 4 and 7, 1927. Symptoms and occult blood disappeared after the second injection and did not return. Later, the gastric analysis was 56 and 80. On the x-ray films the stomach was normal in tone, but the pyloric defect was still present.

CASE 11.—A very sick man, aged 46, presented himself at the clinic complaining of constant pain in the stomach, of inability to eat and of a steady increase in intensity of symptoms of three weeks' duration. Four years before admission, he had had an attack of gnawing pain in the epigastrium which lasted about six weeks but which was temporarily relieved by food and soda. At that time his appetite was good, and he had not lost weight.

On physical examination the man was found to be sick, worn out, in considerable pain and markedly underweight. There was marked spasm of the upper rectus muscles and tenderness on light palpation. The gastric analysis was 52 and 68. The stools contained occult blood. On the x-ray films there was a large defect in the pylorus with a probable perforating ulcer. The patient would not consent to operation; consequently, he was placed on a soft diet and given a nonspecific milk preparation in 10 cc. amounts on April 16, 18, 21, 24, 27 and 30. Pain and bleeding disappeared after the second injection, and the gaseous distention was practically relieved by the end of the treatment. He gained weight and looked well. The gastric analysis was not done, but the x-ray films were unchanged.

Five weeks after the end of treatment the symptoms returned, as did the previous local abdominal pain. The gastric analysis was 72 and 92, and the x-ray films were unchanged. The milk preparation was again given on June 5, 11, 13 and 19 without relief. On June 24 he had a hematemasis and will, I believe, now consent to be operated on.

CASE 12.—A man, aged 47, entered the dispensary complaining of symptoms of two weeks' duration exactly similar in kind but greater in degree than those which brought him to the dispensary one year before when the condition was diagnosed as duodenal ulcer and the patient placed on routine medical treatment and evidently cured. On the return of the gnawing hunger pain, which was temporarily relieved by food, he had reinstated the same procedure but without help. He had lost his appetite and was very uncomfortable.

On physical examination, the man had a pinched face, was somewhat below weight and was quite tender in the midepigastrium. Blood was not found in the stools; the gastric analysis was free acid, 60, total, 84, and the x-ray films showed a large filling defect in the duodenum and an irritable stomach. On May 2, 4, 7, 9, 11, 15 and 18, he was given a nonspecific milk preparation in 10 cc. amounts. The symptoms entirely disappeared after the third injection. He began to gain weight and by the end of the treatment had put on 8 pounds (3.6 Kg.). The x-ray films at this time were unchanged. The gastric analysis was 80 and 110. The condition is cured clinically.

CASE 13.—A negro, aged 37, complained of a gnawing pain in the pit of his stomach; his appetite was good, but he was afraid to eat. The pain awakened him at night, and the attack had been active for ten days. In the previous two years, he had had four or five similar attacks.

The physical examination gave negative results. There was no blood in the stool. The gastric analysis was 58 and 72. The x-ray films showed a filling defect in the duodenum. He was given 10 cc. of a nonspecific milk preparation on May 21, 23 and 28 and on June 4, 7, 11 and 18, 1928. After the second

injection, the symptoms had vanished. At the end of treatment, the gastric analysis was 60 and 90. The defect in the duodenum seemed more pronounced and the stomach more spastic in the x-ray films. He was always on a regular diet and was considered cured clinically.

Case 14.—A man, aged 32, complained of a severe gnawing pain which started in the midepigastrium and at times spread over the entire abdomen. Neither food nor soda gave relief. His appetite was poor, and the pain kept him awake at night. In the two years before admission he had attacks in the fall and spring which lasted four or six weeks, but at these times food or soda gave relief and his appetite was good.

On physical examination, the patient was obviously uncomfortable, looked tired and had lost some weight. There was definite tenderness in the midepigastrium. Examination of the meat-free stool showed the presence of occult blood. The gastric analysis showed a hyperacidity—72 and 94. The x-ray films revealed a tremendously irritable stomach with a filling defect in the cap. On Feb. 2 and 8, 1927, he was given 10 cc. of a nonspecific milk preparation at each injection. Four days after the first injection, he was without symptoms, and he remained so up to the time this paper was written. The gastric analysis was 58 and 96. In the x-ray films the stomach was seen to be much less irritable, but the defect in the duodenum still remained. He had always been on a general diet and after he had regained the 8 pounds he lost prior to treatment, his weight had remained constant.

Case 15.—A man, aged 64, had had innumerable attacks of epigastic pain and discomfort for the past twenty years. The symptoms of which he complained in the present attack had been annoying for six months, and in the past two months he had been desperately uncomfortable with constant, gnawing pain. He had been on a soft diet for months and had lost a great deal of weight; his appetite was poor. During the first attacks the pain had been relieved by food or soda, but in more recent years this had been of no avail.

On physical examination, the man was found to be underweight, sick, tired and anemic. There was a mild generalized psoriasis and marked tenderness and spasm in the midepigastric region. Occult blood was presented in the stool, and x-ray films showed an irritable, dilated stomach with a large filling defect in the duodenum. The gastric analysis was 74 and 92.

On Jan. 2 and 9, 1928, he received 10 cc. of a nonspecific milk preparation. The pain was entirely relieved in three days, and the discomfort due to gas was lessened. Two months later he was without symptoms, and he remained so for six months after treatment, although three months before this paper was written he had an attack of grip. Two months after treatment the gastric analysis was 60 and 70, and the x-ray films did not show any change. At that time he was on a general diet and had gained 14 pounds (6.4 Kg.). At the time this paper was written, the gastric analysis was 30 and 46 and the x-ray films still unchanged, although he looked like a new man.

Case 16.—A man, aged 43, complained of pain in the upper part of the stomach for six months. He had been told that he had an ulcer and was on a soft diet. The symptoms had been intensifying and food, which had relieved him in his three previous attacks during the past two years, was without avail. He had not lost weight, and his appetite had been bad for only two or three weeks.

The physical examination gave negative results except for tenderness in the midepigastric area. The stools did not contain blood, and the gastric analysis showed a free acid of 46 and total of 56. Roentgenogic examination showed a large filling defect in the duodenum.

He was given a nonspecific milk preparation, 10 cc. at each injection, on April 2, 9, 16, 20 and 24 and on May 1, 1928. At the end of treatment his condition was unchanged; the gastric analysis was 60 and 88, and the x-ray plates the same. He was operated on at the Johns Hopkins Hospital by Dr. Dean Lewis, and a large indurated but not unusual duodenal ulcer was found. A gastro-enterostomy gave him complete relief.

Case 17.—A negro laborer, aged 43, complained of pain in the pit of his stomach which was at times relieved by food and at others made worse. Symptoms had been present for three or four weeks, and at times there had been retention and vomiting. Eighteen months before admission, he had a similar attack. At this time, an appendectomy completely relieved him.

On physical examination, he was found to be in good general condition. Nothing unusual was found except mild tenderness in the epigastrium and marked clapotage. Occult blood was present in the stool, and the gastric analysis was 40 and 75. The x-ray report was: ulcer in the duodenum with atonic stomach and partial obstruction.

He was given 10 cc. of a nonspecific milk preparation on April 2, 9, 13, 16 and 19, 1928. At the time of the fourth injection the symptoms had completely disappeared, and the stools did not show any traces of blood. On the night of the first three injections, there had been considerable localized epigastric pain. On April 21, the gastric analysis was 10 and 30; the x-ray films were unchanged. Three weeks later, the gastric analysis was 20 and 52; one of the x-ray films showed the complete outline of the duodenum, but the stomach was still somewhat dilated. At the time this paper was written, he was clinically well and had been on a regular diet for two months.

Case 18.—A man, aged 46, complained of symptoms of four weeks' duration, i. e., a gnawing pain on an empty stomach and sour eructation which at first were relieved by food; later, he was afraid to eat and gaseous distention became a prominent and uncomfortable complication. He had two previous and similar attacks.

The physical examination gave negative results. The gastric analysis was 90 and 112. The stools did not contain blood, and the x-ray films showed a filling defect in the duodenum and an irritable stomach. On June 4 and 11, 1927, he was given 10 cc. of a nonspecific milk preparation. All symptoms disappeared after the first injection, and he remained clinically cured for thirteen months. He was at all times on a regular diet. A second x-ray film was not made.

Case 19.—For six weeks a man, aged 26, had been having a boring pain in the epigastrium which often spread over the entire abdomen and was usually helped by food or soda. He slept well, and his appetite was good. In the previous four years, he had five similar attacks which lasted from four to six weeks.

Physical examination gave essentially negative results. The stools did not contain blood, and the gastric analysis was not done. The x-ray showed a large filling defect in the duodenum. A nonspecific milk preparation was given in 10 cc. amounts on March 6, 10 and 15, 1927. Complete relief from symptoms was experienced after the second injection, and he remained cured clinically. He had always been on a regular diet.

Case 20.—For four weeks a man, aged 42, had severe epigastric pain which was not relieved by a soft diet, antispasmodics and rest. In three previous attacks lasting from four to eight weeks each, his appetite had been good, and the pain had been temporarily relieved by food or soda. He was quite uncomfortable and wanted relief quickly.

On physical examination the man was found to be thin, undernourished, anemic and sickly, with bleeding hemorrhoids and spastic upper rectus muscles. There was marked tenderness over their region. The hemoglobin was 74 per cent (Sahli), gastric analysis 58 and 76, and the stool contained macroscopic blood. On the x-ray films, a large filling defect was seen in the duodenum. The stomach was tremendously irritable. Complete relief from symptoms was obtained after the third of the injections of a nonspecific milk preparation which were given, 10 cc. at a time, on April 2, 5, 8, 15, 18 and 24, 1928. At the end of the course, the x-ray films were unchanged; the gastric analysis was 30 and 76; the hemorrhoids had been benefited by local treatment; he had gained 8 pounds and looked well. He was on a regular diet after the third injection. His cure was permanent up to the time this paper was written.

CASE 21.—A man, aged 30, complained of a gnawing hunger pain in the epigastrium coming on two or three hours after meals and relieved by food or soda. The attack had lasted two weeks and was the fifth successive recurrence of attacks in the fall and spring. His appetite was good, and he had not lost weight.

Physical examination gave essentially negative results. The stool did not contain blood. The gastric analysis was 50 and 70. A filling defect in the duodenum was found in the x-ray films. He was kept on a general diet and given 10 cc. of a nonspecific milk preparation on June 4, 10 and 16, 1927. Three days after the first injection all symptoms left, and he remained clinically well up to the time this paper was written. On July 6, 1928, the gastric analysis was 42 and 64, and the filling defect in the duodenum was much smaller according to the x-ray films.

CASE 22.—A man, aged 30, badly crippled with arthritis, complained of a gnawing feeling in the pit of his stomach. It had been present off and on for six weeks and was at times temporarily relieved by food and at others made worse. More recently, there had been some nausea with retention vomiting at times.

A similar but less severe attack had occurred eighteen months before admission when the patient was in a naval hospital for treatment of the arthritis. There he received intravenous injections of mercurochrome-220 soluble and intramuscular injections of whole milk without benefit to the arthritis or the gastric discomfort. Since he had been under autogenous vaccine therapy, the arthritis had been greatly helped.

The physical examination showed generalized arthritis deformans, slight tenderness in the epigastrium and clapotage. The gastric analysis was 42 and 62, and occult blood was found in the stool. X-ray films showed an irritable stomach and a filling defect in the duodenum. There was considerable six hour retention. Ten cubic centimeters of a nonspecific milk preparation was given May 2, 4, 7 and 10, 1928, and resulted in complete relief from symptoms as well as the gastric retention (as shown by the x-ray films). He was kept on a regular diet.

The patient also volunteered the information that his joints felt less stiff than previously.

CASE 23.—A man, aged 45, had had symptoms for four weeks: a gnawing, boring pain in the epigastrium, more or less constant, usually temporarily relieved by food and accompanied by a great deal of gaseous eructation and distention. For three weeks he had been taking a soft diet, antispasmodics and alkalis, without benefit. Four years before admission, he had a similar attack which lasted for two months.

Physical examination gave essentially negative results. The stools did not contain blood, and gastric analysis was 30 and 48. The x-ray films showed an irritable stomach with a filling defect in the duodenum. A nonspecific milk preparation (10 cc.) was given May 4, 7, 10, 14 and 17, 1928. The pain stopped after the second injection, but the gaseous distention and eructation continued for three weeks. At that time the gastric analysis was 34 and 52 and the x-ray films unchanged. He was on a regular diet and when this paper was written was clinically well.

CASE 24.—In the spring and autumn previous to admission, a man, aged 27, had attacks similar to the present one. This attack had been active for three weeks with boring hunger pains localized in the epigastric area, usually temporarily relieved by food. Medical treatment did not give any help, and the belching and regurgitation had become worse.

Physical examination gave essentially negative results. The stool did not contain blood, and the gastric analysis was 84 and 96. The x-ray films demonstrated a filling defect at the pylorus, with an irritable stomach. He received 10 cc. of a nonspecific milk preparation on May 17, 21, 23 and 25, 1928, and returned home feeling greatly improved. Six weeks later he was in about the same condition. He was on a general diet.

SUMMARY

1. Intramuscular injections of a purified milk protein have been given to twenty-four patients suffering from peptic ulcer.

2. Of these patients, 83.2 per cent have been greatly improved or clinically cured.

(*a*) All of the patients were ambulatory.

(*b*) Pain was the first symptom to disappear.

(*c*) Other symptoms disappeared later.

(*d*) Ten cubic centimeters was given at each injection.

(*e*) There were two mild general reactions.

(*f*) A local reaction occurred in one patient.

(*g*) The majority of the patients were on a general diet.

3. There is no constant rise or fall in gastric acidity following treatment.

4. Great change is not demonstrated by x-ray examination, although spasm may be markedly decreased and the shadow defect appear smaller.

5. It is not suggested that this is a permanent cure. It has been used for too short a time and in too few cases.

6. The nature of the reaction produced by the milk protein is unknown.

OPIUM ADDICTION

II. PHYSICAL CHARACTERISTICS AND PHYSICAL FITNESS OF ADDICTS DURING ADMINISTRATION OF MORPHINE *

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Among the many problems present in connection with opium addiction is one about which there seems to be a good deal of controversy—Does addiction to this drug bring about physical deterioration? A good deal of confusion that exists in the literature on this subject is due, as Terry and Pellens [1] have pointed out, to variation in individual susceptibility and the amount of daily dosage and to the failure to distinguish between drug balance and early withdrawal symptoms.

Opium addicts, when once "hooked," as they so aptly express their plight, need a certain daily dosage to prevent the appearance of "withdrawal symptoms." In certain types of users, this dosage may remain constant in small quantities for years. Another and far more numerous group is composed of those who increase the amount used until eventually they are forced to undergo treatment or begin reduction of the dose themselves. In either event, they must endure some or all of the withdrawal symptoms, which are practically always associated with loss of weight and, according to the addict, extreme weakness.

With this question in mind, we have studied a series of patients who were addicted either to morphine or to heroin. We believe that the underworld type, which constituted the greater percentage of our cases, is the best group for this study as they have been subject to the various factors mentioned by Terry and Pellens [1] which have clouded the issue of physical deterioration and physical fitness. Our studies consisted in measuring the weights, heights and vital capacities, making thorough physical examinations and subjecting the patients to Schneider's test of physical fitness during the administration of a sufficient amount of morphine to supply their needs, and comparing these observations with normal standards.

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* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1. Terry, Charles E., and Pellens, Mildred: The Opium Problem, Camden, N. J., Haddon Craftsmen, 1925.

PHYSICAL EXAMINATION

A careful examination in ninety-six cases together with information gained from the supervision of the physical examination in 450 additional cases by the interns on service gave the following results:

The large majority of the patients were between the ages of 20 and 40 and their physical status conformed closely to that of the normal persons of that age and group. Some showed emaciation which sometimes reached an extreme degree, but many were muscular and well developed and a number were obese.

Fig. 1.—Scar formation: the result of six months' hypodermic administration of heroin.

The skin was sallow in many cases, but this change in color was practically always present in patients who lived a rather unhygienic, sedentary life. On the other hand, the skin of those who followed healthy outdoor occupations had the color of excellent health.

Distribution of hair conformed to that of normal persons. A few showed premature grayness, but the incidence was not out of proportion to that for the general population.

Sixty per cent of these ninety-six patients showed scars of previous abscesses, and 5 per cent had active abscesses on admission to the hospital. These were usually found over the upper arms, abdomen, thighs and buttocks. Several types of scars were noted. The older marks were pale bluish discolorations just below the skin which the patients declared were due to cocaine. The more recent marks were the result of abscesses caused by improperly disinfected hypodermic needles or by the irritating diluents used with either morphine or heroin; the average diameter of the abscesses was about 4 cm. The abscesses when healed left depressed, cicatrized scars. The subcutaneous tissue of the arms, thighs and abdomen was quite frequently the seat of a good deal

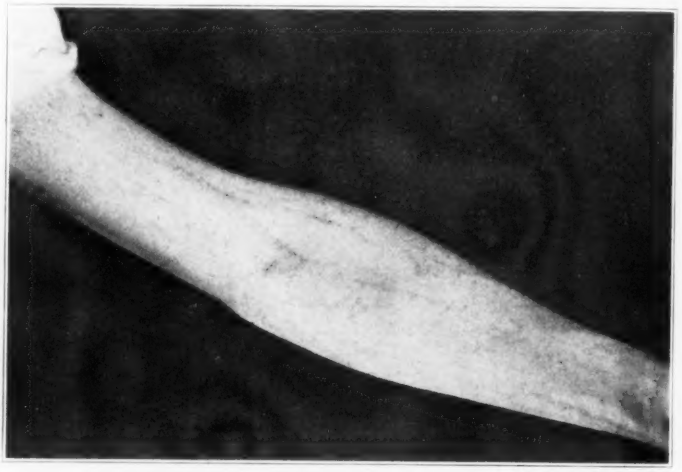

Fig. 2.—Points of injection with discoloration over superficial veins of forearm and arm, in addict using 20 grains (1.3 Gm.) of morphine intravenously daily for a period of six months.

of induration, and often small, isolated, nodular masses could be palpated. We have seen one case of tetanus develop from suppurating abscesses.

The pupils were practically always contracted when the patient had had his usual quantity of the drug. They reacted to light and in accommodation, though somewhat more sluggishly than normally. In three patients (3.3 per cent) who had been addicted for periods of more than ten years, the contraction of the pupils was absent during administration of the drug. The extra-ocular movements were normal. The eyegrounds did not show any abnormality of either the retina or the vessels.

The nose rarely (2 per cent of our cases) presented a perforated septum as a result of the patient sniffing cocaine. In 40 per cent of our cases we encountered considerable congestion of the nose and nasopharynx with increased secretion and consequent difficulty in breathing through the nostrils.

Sixty per cent of the ninety-six patients examined exhibited a particularly high degree of pyorrhea and dental caries. Before attributing these changes to the continued use of drugs, one must bear in mind that these people are notorious in their lack of care of the teeth and

Fig. 3.—Active abscesses, the result of two months' hypodermic injections of 70 grains (4.5 Gm.) of heroin daily by a fellow addict.

failure to consult a dentist. Two per cent had suppurating abscesses about the teeth. A tremor of the tongue was present in 4 per cent of the patients examined. Otherwise, the oral cavity showed nothing abnormal. The throat (40 per cent) showed a chronic inflammatory condition, but these persons are excessive smokers, a factor to be borne in mind.

The thyroid was not palpable in a single case. The chest was, as a rule, of normal shape with good expansion. In four cases inactive fibroid tuberculosis was present, which was confirmed by roentgen examination. The heart was normal in size as determined by percussion, and the apex beat was in the normal position. Thrills were not present

on palpation in any case. Heart sounds were of good quality, and in only one case of the ninety-six was a systolic mitral murmur present, with no evidence of cardiac decompensation. The heart rate was slow in most cases, the average being 68 beats per minute. There was evidence of sclerosis of the peripheral vessels in only one patient, a man, aged 64, who had a degree of sclerosis consistent with his age. He had been using morphine for thirty-two years.

The abdomen was soft and enlargement of the liver or spleen was not noted, nor were we able to elicit any tenderness in the liver. Fecal masses were often palpable in the descending colon. The extremities were, as a rule, poorly developed, except in patients who performed manual labor or engaged in exercise; in such persons the extremities were proportionately developed. Definite tremor of the outstretched hands was encountered in 4 per cent of our cases. The degree of staining of the fingers due to cigaret smoking is extreme.

WEIGHTS AND VITAL CAPACITIES

Methods.—One hundred men were examined for age, weight and height, and comparisons were made with figures considered normal by the Mutual Life Insurance Company of New York. An allowance of 5 pounds (2.3 Kg.) was made for the weight of clothing in the insurance weight tables. Vital capacities were determined in eighteen cases and were compared with Dreyer's table,[2] both actual weights and normal weights for height and age being used.

Weights and Vital Capacities of Opium Addicts During the Administration of Morphine

	Number of Cases Above Normal	Number of Cases Below Normal	Highest Value, per Cent	Lowest Value, per Cent	Average for Group, per Cent
Weight compared with normal weight for height and age..	43	53	+35	−24	+ 0.2
Vital capacity compared with Dreyer's normal using observed weight					
Dreyer's class B.....	10	8	+22	−30	+ 2.6
Dreyer's class C.....	12	6	+32	−25	+ 9.6
Using subject's normal weight for height					
Dreyer's class B.....	10	8	+22	−17	+ 3.4
Dreyer's class C.....	15	3	+30	−11	+10.5

Results.—Ten persons in the group of 100 studied, whose height and weight were measured, varied 20 per cent from the normal weight for the age and height; these ranged 35, 31, 29, 28, 26 and 21 per cent above and 25, 24, 24 and 24 per cent below. The average weight above normal in the forty-three cases above the mean normal was 18 pounds

2. Dreyer, Georges, and Hanson, G. F.: The Assessment of Physical Fitness, London, Cassell & Co., 1920, pp. 115.

(8.2 Kg.), the average weight below normal in the fifty-three cases below the mean normal was 19 pounds (8.6 Kg.). The average of the entire group of 100 cases was only 0.2 per cent above normal. The average length of addiction of the patients showing weights above the normal figures was 10.5 years, with an average daily dosage of either heroin or morphine of 21 grains (1.36 Gm.). The average length of addiction of the persons with weights below normal was 9.5 years, with a daily consumption of 22 grains (1.4 Gm.) of drugs.

Vital capacities in eighteen cases were compared with Dreyer's classes, which are as follows:

Class A: Army and Navy personnel, and any person who has undergone prolonged training in either service independent of his ordinary vocation in life.
Police force.
Athletes and active sportsmen.
University students (playing games).
Fire brigade.
Blacksmiths and boilermakers.

Class B: Professional classes (doctors, lawyers, etc.).
Business men.
Railwaymen.
High grade mechanics.
Clerks, upper class.

Class C: Tailors.
Shopkeepers.
Shoemakers.
Printers.
Potters.
Clerks, lower class.
Painters.

Our subjects classified as to occupations according to their own statements, which of course are subject to question, were: four chauffeurs, two bookbinders, one salesman, one farmer, one printer, one driving instructor, one draftsman, one foreman in a garage, one miner, one cook on a ship, one railroad employe, one brass finisher, one reporter and one unknown. They belong, therefore, in Dreyer's classes B and C. No constant significant deviation from the normal was observed; the vital capacities, when they varied from the normal, tended to be high rather than low for classes B and C.

PHYSICAL FITNESS

Schneider's test [3] was applied thirty-one times on twenty-one subjects during the administration of morphine. The resulting scores range from 1 to 17. In seventeen of these subjects the scores range from 10 to 17.

3. Schneider, Edward C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

The remaining four cases scored as follows: one case, 9 points; the second case, 8 and 12; the third, 1 and 5 and the fourth case, 6, 4 and 11. A perfect score indicating the ideal physical fitness is 18 points.[3] The test is based on pulse rates taken while the patient is reclining and standing, a comparison of the two, changes in blood pressure while the patient is reclining and standing and the increase in heart rate after slight exercise as well as the speed of return to normal.

Our subjects all scored well in the various determinations necessary except for the change in pressure when they changed from the reclining to the standing posture; in practically all cases, there was a tendency to a fall rather than a rise in pressure. Schneider [4] attributed this in many cases to excessive cigaret smoking, which invariably is noted in our cases. The low score of only 1 point obtained in one of our cases was in a person who was extremely neurotic but who did not show evidence of organic disease. There is no correlation between the various scores and length of addiction, daily dosage and age. Schneider [4] considered a score below 9 points as indicative of organic disease or unhygienic living.

COMMENT AND LITERATURE

We have been unable to find in the literature any data on actual weights, heights, vital capacities and tests of physical fitness in the opium addict. The various statements made in reference to opium addiction and its effects on physical appearance and physical fitness apparently are based on limited inspection. Levinstein,[4a] Osler [5] and Lambert [6] agreed that the drug may be used for months before any signs of emaciation appear. Osler [5] and Lambert [6] also stated that some persons can use the drug for several years without showing emaciation. Kraepelin [7] called attention to the fact "of how little the symptoms of the disease may catch the eye." Bishop [8] advanced the theory "that the same power which locked up the opiate in the body also locked up the toxic products of tissue metabolism." According to Bishop,[8] if the addict

4. Schneider, Edward C., and Truesdell, Dorothy: Daily Variations in Cardio-Vascular Conditions and a Physical Efficiency Rating, Am. J. Physiol. **67**:193 (Dec.) 1923.

4a. Levinstein, Edward: Die Morphiumsucht, tr. by Charles Harrer, 1878.

5. Osler, W.: The Principles and Practice of Medicine, 1894, ed. 6, New York, D. Appleton & Company, 1905, pp. 1160.

6. Lambert, A.; In Nelson's Looseleaf Medicine, New York, Thomas Nelson & Sons, 1920.

7. Kraepelin, Emil: Lectures on Clinical Psychiatry, tr. from ed. 2 (German) rev. and ed. by Thomas Johnstone, ed. 3, London, Bailliere, Tindall & Cox, 1913.

8. Bishop, Ernest S.: Narcotic Drug Problem, New York, The Macmillan Company, 1920, p. 47.

maintains "good elimination" he will escape detection and not show any signs of physical deterioration for years. In the few recognized cases of opium addiction that have come to autopsy, whether the drug was being taken at the time of death or not, the pathologic changes found have been insignificant (Ball,[9] Anders and Musser,[10] and Allbutt [11]).

Bishop [8] and Morat [12] both stated that they found not only enlargement of the liver, but tenderness over this area during addiction. We have been unable to confirm this observation in any case in which morphine was being administered in sufficient quantities to prevent withdrawal symptoms. The contracted pupils are by far the most constant physical sign, as most observers state, and may justify one in considering the possibility of addiction.

We do not doubt the existence of the extreme cases of emaciation reported in the literature. It is inevitable that some users of opium will at a certain time in their lives reach this degree of physical impairment. Sooner or later, the great majority exhaust their funds, and it becomes a matter of either drugs or food. At this point they invariably purchase drugs. They tend then to resort to cures or to attempt themselves to reduce their dosage, with consequent withdrawal symptoms.

This point is best illustrated by one of our patients who immediately after his first treatment in our ward again began the use of the drug when discharged from the hospital. Within a period of two months, during which time he was unable to obtain a sufficient amount of the drug and sufficient food, he lost 30 pounds (13.6 Kg.). He then returned to our ward where the drug, in quantities sufficient to prevent withdrawal symptoms, and abundance of food were administered for several days before treatment was begun. He showed a rapid gain in weight in this short period before treatment.

There is a direct ratio between the decline in strength and weight and the number of times the addict curtails his food in order to get the drug. We agree with the statement of Bishop [8] that if the drug is used in sufficient amounts in relatively normal hygienic surroundings, the opium addict will escape detection for years and will not show any obvious physical deterioration or impaired physical fitness.

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9. Ball, B.: Des lésions de la morphinomanie, et de la presence de la morphine dans les viscères, Encéphale, 1887.

10. Anders, J. M., and Musser, J. H.: Practice of Medicine, Philadelphia, W. B. Saunders Co., 1920.

11. Allbutt, Thomas C.: A System of Medicine, London, The Macmillan Company, 1905.

12. Morat, D.: Le sang et les secretions au cours de la morphinomanie et de la desintoxication, Paris, G. Steinheil, 1911, p. 180.

CONCLUSIONS

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine.

We believe that the existence of considerable emaciation in certain cases is caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug.

THE VENTRICULAR ELECTROCARDIOGRAM

AN EXPERIMENTAL STUDY *

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The experimental work on the ventricular electrocardiogram by Rothberger and Lewis and their co-workers, Wilson and Herrmann,[1] Smith,[2] and others, indicates that the principal divisions of the electrocardiogram, namely, the QRS complex and the T wave, may not be commonly or equally affected under abnormal conditions, and that this is because the QRS represents the excitation and the T wave the retreat of the process by virtue of which the contraction occurs. The practical value of the unequal response for differential diagnosis suggested an investigation of the curve of the ventricle from this angle and the report which follows is concerned with the nature of the disturbances required to affect the component portions of the ventricular electrocardiogram; in other words, the relation of the changes in the QRS (an in this connection also the associated question regarding arborization block was involved), the T wave and the RT period, to the injury or destruction of heart muscle. When coronary vessels are closed a close parallel between the changes in the muscle and the T wave of the electrocardiogram does not exist, although right and left ventricular effects are associated with opposing actions on the T wave.[3]

METHOD

Forty experiments were performed on dogs under chloretone narcosis, section of the vagus nerves, artificial respiration and the heart exposed by removing the sternum. The heart muscle was destroyed by the injection of 95 per cent solution of alcohol. In some of the experiments, bundle branch block was induced in order to compare the effect of the injections with those in which conduction through the bundle was undisturbed. The electrocardiograms were taken with axial (R.A.-L.L.) and transverse (across

* Submitted for publication, Oct. 20, 1928.

* From the Laboratory of Physiology, Faculty of Medicine, Paris.

1. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920; An Experimental Study of Incomplete Bundle Branch Block and the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.

2. Smith, F. M.: Experimental Observations on the Atypical QRS Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**:205 (Aug.) 1920.

3. Otto, H. L.: An Experimental Study of the Extracardial Nerves: IV. The Coronary Arteries, Heart **3**:691 and 697, 1928; Ueber die Beziehungen der Accel. zur den Folgen der Unterbunding von Coronargefässen, Arch. f. d. ges. Physiol. **37**:528, 1927.

the thorax, and perpendicular to the axial) leads. The effect of making small variations in the line of the leading was also studied in many of the experiments. The electrodes employed were heavy copper pins, and the line of the leading could be varied without disturbing the primary lead by the insertion of other electrodes.

RESULTS

Extensive destruction of the heart muscle in the dog can be made before it causes circulatory failure. The injection of an irritant like hypertonic saline solution into the muscle does not significantly alter the electrocardiogram. These were observations also made by Eppinger and Rothberger,[4] who first studied the effect of this type of injury to the heart. Therefore, the electrocardiographic changes which occur from injections of alcohol are solely due to the destruction of the muscle, irritation of the muscle playing no part. In this connection two further points of interest appeared, namely, that mechanical irritation of the ventricular muscle was also without effect on the electrocardiogram, and, the amount of injection which was usually necessary to affect the T wave permanently was considerably less than that required to affect the QRS. Contrasted to the T wave, this portion of the electrocardiogram was stable and did not give indication of the changes, i. e., the destruction of muscle, which had taken place within the myocardium.

THE CHANGES IN THE T WAVE

The injection into the muscle of the right ventricle tended to cause negativity of the T wave and the ST fusion, although this was rarely pronounced, even when the injection of the right ventricle was extensive. This observation was also made by Eppinger and Rothberger.[4] Frequently an injection into the conus region or in the upper corner of the right ventricle on the right margin of the heart caused the temporary elevation of the T wave and RT fusion.[5] No portion of the right ventricle had a specific influence on the T wave. The effects of injection into the conus, apex, central and right upper portions were compared. The effect produced on the T wave was occasionally positive in one lead. Discordant effects could be made concordant, however, without affecting the direction of the QRS by altering the line of the leading (not its direction). This was also observed [6] with regard to the action of the accelerator nerves on the T wave.

4. Eppinger, H., and Rothberger, C. J.: Zur Analyse des Elektrokardiograms, Wien. klin. Wchnschr. **22**:1091, 1909.

5. By RT fusion is meant the peculiar form of electrocardiogram in which the T begins before the complete descent of the second limb of the spike R to the iso-electric line. ST fusion is the obverse form.

6. Otto, H. L.: An Experimental Study of the Extracardial Nerves: I, Heart **3**:691, 1928.

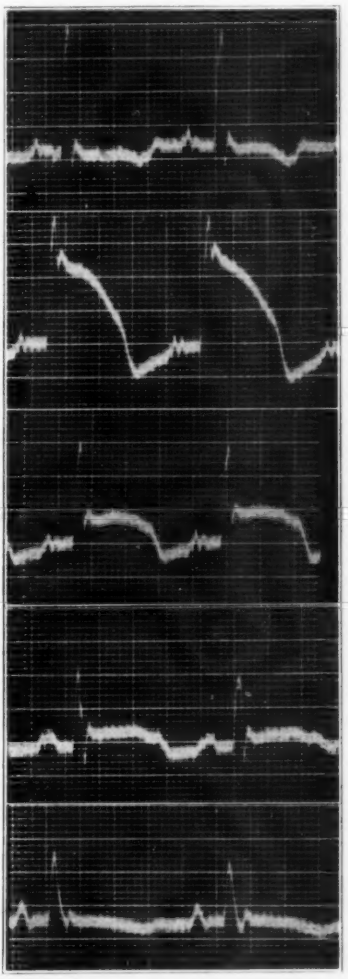

Fig. 1.—Axial (R. A.-L. L.) leading, time in fiftieth seconds. *A* is the normal, *B*, *C* and *D* the changes which followed destruction of muscle in the left ventricle. The curves were taken immediately, five and ten minutes after the injury. *E* represents a permanent increase in the QRS time which followed destruction of muscle in the septum in the region of the left bundle. Note the final change in the RT interval from the injury to the left ventricular muscle (*D*).

Injection into any portion of the left ventricle caused the immediate appearance of the exaggerated RT fusion which Eppinger and Rothberger [4] reported. This was not a permanent effect, however, but receded in a few minutes to the original form of the electrocardiogram or to one which differed from it by the elevation of the RT interval above the iso-electric line, associated with an increase in the positivity of the T wave (fig. 1). Since an irritation of the muscle from the injection will not explain the earlier effect, the latter must be the result of a transient, widespread paralysis of muscle function.

The degree of permanent change in the RT interval and T wave depended on the line of the leading as well as on the amount of muscle

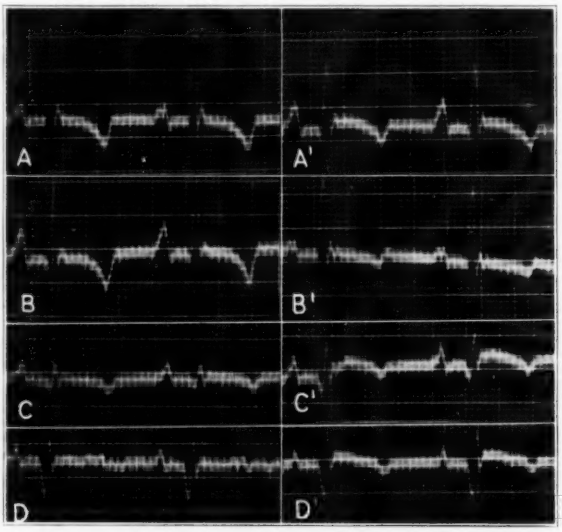

Fig. 2.—Time in fiftieth seconds; *A* is the axial (R. A.-L. L.) lead; *B*, transverse lead; *C*, transverse lead, with the right electrode placed higher in the wall of the right side of the chest; *D*, right electrode placed lower in the wall of the chest. *A'B'C'D'* indicate the alteration in the form and direction of the T wave after destruction of a small area of muscle in the wall of the left ventricle. Note how the line of the leading favors the appearance of RT fusion, *C'*.

destroyed by the injection, since small variations in the latter (often involving a change in the line of the leading not more than 30 degrees) altered the form and direction of the T wave or presented variations not observed in the other leads (figs. 2 and 3).

A comparison of the effect of injection into the various portions of the left ventricle (the base, apex, papillary muscles and interpapillary regions) indicated that involvement at the basal portion of the

left ventricle did not induce enduring RT fusion, but that the injection into the apex or the interpapillary region frequently did so, and that the area of muscle destroyed which most uniformly yielded this effect was the interpapillary area and the adjoining portions of the bases of both papillary muscles. Sometimes only a small area of injection in this location was necessary to induce the RT fusion, one which did not destroy the entire thickness of the wall or involve the endocardium. The second branch from the circumflex division of the left coronary artery usually supplies this portion of the left ventricle, and

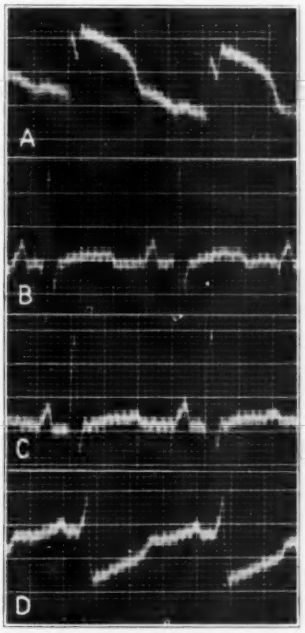

Fig. 3.—Time in fiftieth seconds. *A*, *B*, *C* and *D* are the same lines of leading as in figure 2. This electrocardiogram was taken immediately after the injection into an area of muscle at the upper right corner of the right ventricle. Note the differences in the recorded effect when the line of leading is altered.

the frequency with which this electrocardiogram was found to occur after the ligation of this vessel [3] confirms the observation.

Stimulation of the left accelerator nerve increased the RT fusion, whereas the stimulation of the right nerve lessened it, causing the descending limb of the R spike to descend closer to the base line before the beginning of the T wave, associated with a diminution in the height of the T, from which it may be inferred that the action of the accelerator

nerves on the T wave of the electrocardiogram is not altered in the presence of myocardial injury or an abnormal type of electrocardiographic curve.[7]

The line of the leading was also one of the conditions of importance in favoring the appearance of this form of electrocardiogram when other conditions were predisposed to it (figs. 2 and 3).

Greatly disturbing the heart by inserting a small knife into the left ventricle and injuring the septum caused it to disappear from the axial lead (its appearance in other lines of lead was not investigated). The R wave then descended to the base line or below it before the beginning of the T wave. These observations suggest that its appearance depends on a particular balance or sequence in the order of excitation and retreat in the myocardium.

Injection into the septum was tested in six dogs, but the effect of the destruction of the muscle of the septum was not satisfactory; bundle branch block was the constant result of the injection whenever a large area of the muscle of the septum became involved.

THE CHANGES IN THE QRS

Voltage and Notching.—Although the extensive destruction of the muscle of the myocardium was frequently associated with a diminution in the voltage of the QRS, it occurred as a rule with notching. However, primary diminution in the voltage can occur from a great decrease in the volume of active muscle. Diminution in the voltage followed the extensive destruction of the heart muscle when bundle branch block was present, and also, under the same conditions, there was diminution in the voltage of premature beats elicited from the conus region without a change in their form. But the amount of muscle which it was necessary to destroy in order to affect significantly the voltage of the electrocardiogram was too extensive to justify the deduction that this can be a cause of a low voltage when it is present in the human electrocardiogram. The conclusion was inevitable that the actual amount of gross injury a heart sustained up to the point of causing the failure of its function is a factor of minor importance in the determination of the voltage of its electrocardiogram. The common experimental association of an excellent voltage and cardiac beating so feeble that it is barely visible is also indicative of the same conclusion (fig. 4).

The appearance of notching in association with the diminished voltage indicates that frequent and rapid changes in the position of the electrical axis of the heart are occurring.[1] This is the effect anticipated from the destruction of large or scattered areas in the myocardium. However, the inference from an electrocardiogram presenting notching

7. This is also the case when coronary vessels are ligated.

that the changes in the electrical axis are the effect of changes occurring in the heart muscle is hardly justifiable until it is certain that an altered position of the heart with reference to the leads is not responsible for it.[8] Figure 5 illustrates the appearance of a complicated notching in the transverse lead obtained by a slight alteration in the line of the leading, and figure 6 is one in which the line of leading is unchanged but the position of the heart is altered. The conditions surrounding the appearance of notching were unrelated to the QRS time.

Alteration of the Direction of the QRS.—A great diminution in the functioning muscle of the ventricles did not vary the principal direction

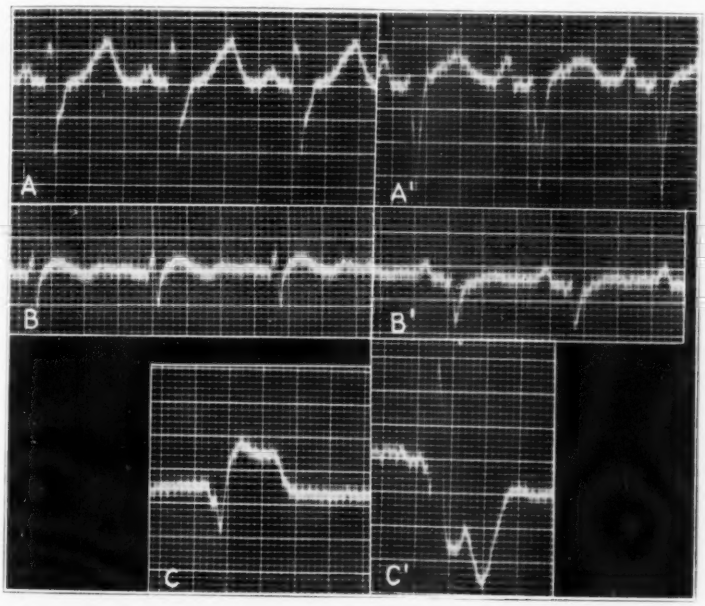

Fig. 4.—Time in fiftieth seconds. The right branch of the bundle has been cut. *A* is the axial lead; *A'*, the transverse lead; *B* and *B'* are these leads after the destruction of practically all the muscle of the external wall of the right ventricle. Note the diminished voltage and QRS time. *C* and *C'* are these leads after destruction of muscle in the left ventricle and circulatory failure. The voltage is greater than when the heart was beating with good force and maintaining the circulation.

8. It is to be noted in passing that another cause of notching exists, namely, an altered conduction order through the branches of the bundle. The section of one of the main divisions of the left branch of the bundle of His, for example, may produce notching in either the transverse or the axial lead when it does not alter the direction of the QRS (fig. 9).

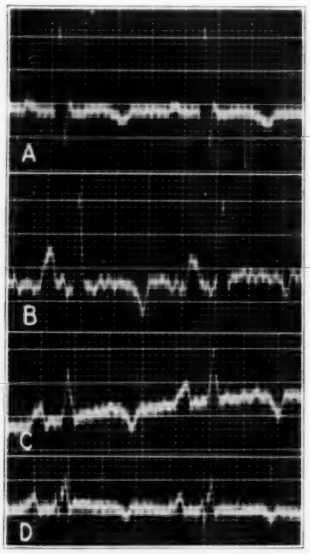

Fig. 5.—Time in fiftieth seconds. *A*, *B*, *C* and *D* show the same lines of leading as in figure 2. Complicated splintering with diminished voltage dependent on the line of the lead.

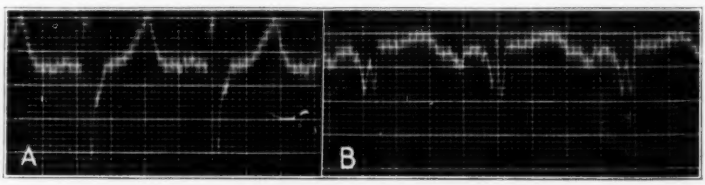

Fig. 6.—Time in fiftieth seconds, axial leading. The right branch of the bundle has been cut, and the second figure shows the effect of altering the position of the heart with reference to the line of the leading. The cardiac apex was tilted upward and to the right. (The equivalent of a counter-clockwise rotation on the transverse axis of the heart.)

taken by the curve. . . . This receives confirmation in the effects obtained when coronary vessels are ligated,[9] whereupon large areas of muscle are thrown out of function without influencing the direction of the QRS. In this connection, it is of interest to note that although the ratio between the weights of the right and left ventricles of the dog (excluding the septum) presents considerable variation which follows the weight of the dog,[10] the direction of the QRS is always upright. It is probable that "preponderance" curves when they do not involve an alteration in the position of the heart with reference to the leads must be explained on the basis of the excitation order within the heart without regard to the masses of muscle involved.

The QRS Time.—As already mentioned, the only significant effect of injection into the muscle of the septum was the appearance of a bundle branch block. Since the injections into the outer walls of the right or left ventricles never resulted in bundle branch block or an increase in the QRS time, it could only be the effect of an injury to the bundle or its branches and not the muscle of the septum. This was further tested in six experiments by making an extensive injection around the points at which the main branches of the bundle reach the external walls of the ventricles, namely, the central region of the right ventricle, the papillary muscles, the junction of the left ventricular wall and the septum at its upper and middle thirds. In one of three animals into which an injection was made into the central region an increase in the width of the QRS with a form resembling that of right bundle branch block occurred after several of the injections, which endured after each injection for a few minutes only before the QRS time was again normal (fig. 7), but the widest possible injection which did not involve the septum would not induce a permanent increase in the QRS time in any of the experiments. To the contrary, a distinct tendency exists for the QRS time to be diminished after the extensive destruction of the myocardium (fig. 4).

In figure 7,f, the small QRS time after the section of the right bundle followed by a decisive increase when one of the divisions of the left bundle has been severed suggests that the right bundle has not been completely severed in this instance. This, however, was not the case because the postmortem examination showed that the right branch was completely severed. The peculiar form of electrocardiogram which this illustration reveals, the appearance of a QRS

9. Lewis, T.: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, Heart **1**:98, 1909. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918. Otto (footnote 3).

10. In the lighter dogs it inclines toward equality, and in heavy dogs it greatly favors the left ventricle.

time less than is expected with right branch block associated with a QRS wave downwardly directed, the last stroke of which fuses without clear demarcation into a markedly positive T wave, was the characteristic curve in the axial lead when the combination of right branch block and the changes giving rise to the RT fusion were present.

ARBORIZATION BLOCK

In 1917, Oppenheimer and Rothschild [11] described a type of abnormal electrocardiogram which they called arborization block because the hearts which gave this curve presented a patchy sclerosis involving the subendocardial muscle and Purkinje tissues when they were examined post mortem. The specific electrocardiographic criteria for the recognition of the condition were widening, notching and low voltage of the QRS, with the absence of the diphasic curves and the huge T wave,

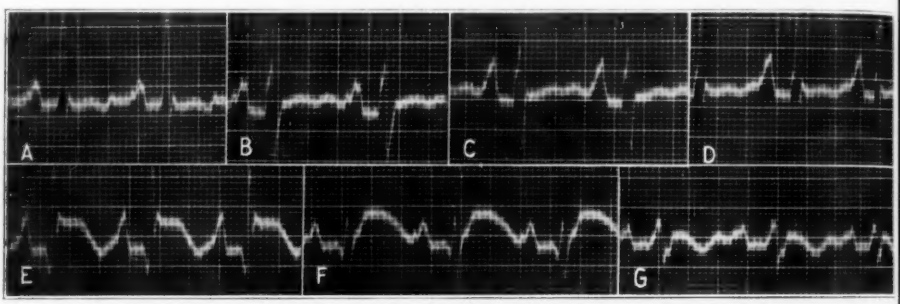

Fig. 7.—Time in fiftieth seconds, axial leading; *A* is the normal; *B*, immediately after extensive destruction of the muscle in the central region. The QRS is widened, the curve suggests the presence of right branch block. *C*, recovery to the normal QRS time; *D*, recovery of the original QRS form, slight splintering and an insignificant change in the T have occurred; *E*, after extensive destruction of the muscle of the left ventricle (the base of the papillary muscles and the area at the junction of the septum and left ventricle at its middle third); *F*, after section of the right branch of the bundle (note the appearance of a normal QRS time); *G*, section of one of the principal divisions of the left branch of the bundle.

opposite in its direction to the main deflection, which are seen with experimental branch block.

That an electrocardiogram like this, however, may be persistently present without finding the pathologic process described to account for it has been pointed out by Drury.[12] Experimentally, Wilson and Herr-

11. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

12. Drury, A. N.: Arborization Block, Heart **8**:23, 1921.

mann were unable to obtain curves resembling these by the section of the minor subdivisions of the branches of the bundle of His, nor at any stage of the transition between the normal complex and complete bundle branch block; Smith [13] caused extensive injury with fibrosis of the heart involving the endocardium without being successful in reproducing this type of electrocardiogram. Sherf [14] observed electrocardiographic forms resembling arborization block in badly damaged hearts at certain stages of the transition complexes when serial premature beats induced from the external walls of the ventricles were interfering with beats supraventricular in origin, and he concluded that arborization block was due to an incomplete block in one of the branches of the bundle associated with injury to the smaller divisions of the other branch of the bundle.

The most significant of the electrocardiographic criteria for arborization block is the increase of the QRS time. This could not be experimentally obtained by the section of the minor subdivisions of the branches of the bundle by Wilson and Herrmann,[1] nor by Rothberger and Winterberg,[15] although the latter investigators studied the effect of section of the principal branches of the bundle of His in great detail. Smith [16] was not more successful in obtaining it as the result of wide injury to the endocardium. In the comparison of the effect of section of the subdivisions of the branches of the bundle in a series of twenty-eight experiments I observed that a significant increase in the QRS time never occurred unless complete section of the bundle or all of its subdivisions to one of the ventricles was present, which is in accord with the observations of the previous investigators on the subject. Since the Purkinje network is no longer continuously available for the excitation only when a complete section of one of the two divisions of the bundle has occurred the increase in the QRS is the expression of the extra time required for the excitation to travel through the slower conducting heart muscle of the septum. On the other hand, destruction of the muscle or the endocardium which contains the Purkinje network to the point of circulatory failure will not induce an increase in the QRS time unless it involves an extensive injury to the septum in the region in which the primary branches of the bundle are known to pass, or an injury to all of the bundle of His which supplies one ventricle, or, as suggested by Smith, unless it is associated with myocardial fatigue, under which circumstances all

13. Smith (footnote 9, second reference).

14. Sherf, D.: Zur Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, Ztschr. f. d. ges. exper. Med. **51**:816, 1926.

15. Rothberger, C. J., and Winterberg, H.: Exper. Beiträge zur Kenntnis der Reizleitungsstörungen, usw., Ztschr. f. d. ges. exper. Med. **17**:264, 1916.

16. Smith (footnote 2, and footnote 9, second reference).

conduction, both in Purkinje tissue and in ordinary heart muscle is in all probability also slowed. The experimental evidence makes it reasonably certain that a significant widening of the QRS does not ordinarily appear except by the complete elimination of one branch of the bundle, and this becomes the more unlikely to occur as the branch in question progresses in its subdivision. Suggestive in this connection is the early subdivision of the left bundle and the rarity with which left bundle branch block is seen in the clinic, and the comparative difficulty with which left bundle branch block is experimentally produced in the dog. When an arborization block curve is present, the presence of a complete bundle branch block must be assumed in order to account for the abnormal width of the QRS.

Notching, as Wilson and Herrmann [1] have pointed out, represents the occurrence of frequent and rapid changes in the position of the electrical axis of the heart and is greatest in the lead with the lowest voltage. These criteria therefore will appear together. They can be experimentally produced in the electrocardiogram of the undisturbed heart by shifting the line of the leading into a position which presumably favors a frequent change in the electrical axis with reference to the line of the leading (figs. 5 and 6). Under these conditions, the notching becomes especially pronounced in the presence of the section of one of the two divisions of the left bundle and the complete section of the right bundle. This makes the excitation issue to the ventricle through one strand of the bundle instead of three, and an exaggeration of the effect may be expected since changes in the electrical axis are also exaggerated, and the wide QRS facilitates the clear inscription of the notching (fig. 9).

The differences in the T wave in arborization block and bundle branch block do not appear to be an important differential criterion when it is remembered that the T wave is also greatly diminished in size in a lead which yields low amplitude with notching and that a small alteration in the line of the lead will often alter its direction entirely without affecting that of the QRS.

Figures 7, 8 and 9 are curves obtained by sectioning the right branch of the bundle and of one of the divisions of the left branch.

It is suggested that the electrocardiogram which is termed arborization block is a bundle branch block involving the entire right bundle and part of the left bundle associated with a change in the position of the heart, probably a postero-anterior rotation, i. e., rotation on the transverse axis of the base. The effect of this type of alteration in the position of the heart, it has been suggested elsewhere,[17] is to cause a diminished voltage in all leads.

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17. Otto, H. L.: The Effect of Altering the Position of the Heart upon the Electrocardiogram, Proc. Soc. Exper. Biol. & Med. **26**:4218, 1928-1929.

An increased QRS time can result from destruction of the muscle of the septum when the latter completely involves at least one branch of the bundle. The injury which does this may be grossly in evidence as in the case of obstruction to a coronary artery, or it may be chronic and widely diffused as with arteriosclerotic conditions or finally, localized, minute and undetectable as in most instances of bundle branch block. It is evident that a specific pathologic process cannot be associated with an electrocardiogram which rests

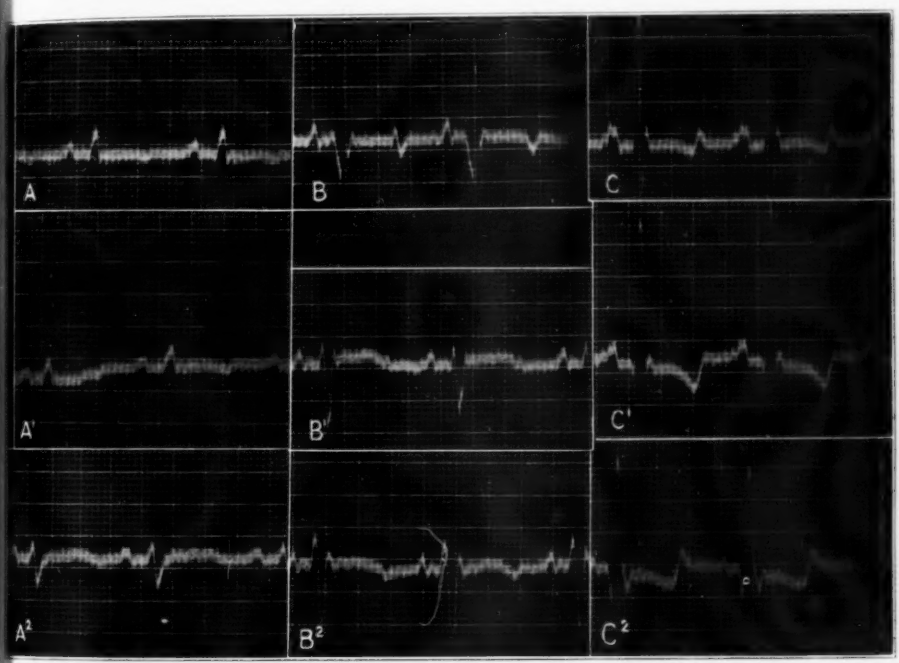

Fig. 8.—Time in fiftieth seconds, *A*-R. A.-L. A. (corresponding to derivation I). *B* is the transverse lead across the thorax; *C*, the axial lead. *A'*, *B'* and *C'* are the same after section of the posterior division of the left branch of the bundle. The QRS changes in form although a normal QRS time persists. *A"*, *B"* and *C"* show these leads after section of the right branch of the bundle. Discordant bundle branch block curves are present (with only one branch of the bundle sectioned they are practically always concordant). Note the absence of the other characteristic features of unimplicated monolateral bundle branch block.

on special conditions of conduction and relations to the plane of the leading. That it is frequently associated with an old infarct from the closure of the descending division of the left coronary artery is readily

understood since this branch extensively supplies the muscle of the septum in the region traversed both by the right bundle before it begins its subdivision and by the anterior division of the left bundle.

COMMENT

The T wave is the more sensitive index of the changes which occur within the myocardium. To affect permanently the T wave the amount of tissue destroyed was much less than that necessary to affect the QRS. Whether this difference is grounded in the difference in the physiologic processes which these portions of the curve represent, or is merely due to the fact that the slow inscription of T gives evidences of change which are hidden by the rapid movement of the string when the QRS is written is beyond the scope of the observations.

The most constant effect on the electrocardiogram caused by the destruction of heart muscle was the shift of the RT interval from the iso-electric line, which is experimental evidence for the importance

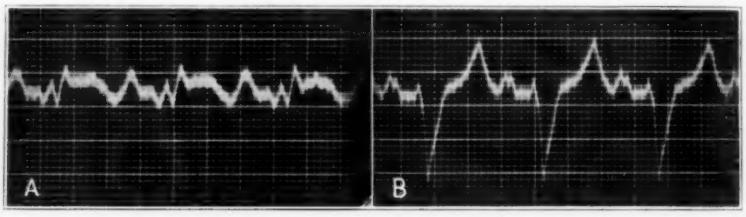

Fig. 9.—Time in fiftieth seconds; complete section of the right branch of the bundle, section of the anterior division of the left branch with some injury to the remaining division of the left bundle. *A'* is the transverse lead (in this animal the R. A.-L. A. lead gave a similar curve); *B*, the axial lead. There is marked notching in the transverse lead, and the QRS is abnormally wide (the dog weighed 25 Kg.). This is again a discordant curve, but the reversal of the discordance of figure 8.

with which this change is regarded clinically. No value could be attached to any of the other changes in the RT period associated with it and the form of the T wave, when the distinctive ST and RT fusions (which are exaggerations of this shift of the RT portion of the curve from the iso-electric line) are disregarded, did not appear to hold a position of importance.

The destruction of the muscle of the right ventricle tended to cause negativity of the T wave in contrast to destruction of the muscle of the left ventricle, which caused positivity of the T. This relation of the two halves of the heart, the right and upper versus the left and lower portions, to the T wave of the electrocardiogram is further substantiated by the effect of ligation of coronary arteries,[3] and the

effects obtained when cooling the heart muscle is compared to freezing it.[18] But the ease with which an altered line of leading alters the direction of the T wave when comparatively small areas of muscle are destroyed make it doubtful if the direction assumed by the T wave when injury is known to be present may be used to infer the location of the injury. It suggests, however, that in searching for evidence of injury to the heart as indicated by alterations in the T wave it might be of aid to have recourse to leads from the chest and to observe the curve through several lines of lead, compassing more cardiac diameters than the leads from the points of Einthoven triangle. These are all within the one plane.

Since an irritation of the myocardium does not have an effect on the form of the electrocardiogram, it may be assumed that inflammatory conditions of the epicardium or myocardium which do not involve the conduction system or inhibit the functioning of the muscle are without effect on the form of the curve and significant alterations of the curve, excluding the action of the extracardial nerves, are probably indicative of depressive or destructive processes.

A substantial increase in the QRS time was unassociated with the destruction of the ordinary heart muscle or the endocardium, which contains the Purkinje network, but was constantly related only to involvement of an entire branch of the bundle or all of its subdivisions to one or the other of the ventricles. Since significant QRS widening does not occur if a subdivision of a branch of the bundle remains to supply the ventricle in question its presence may be taken as good evidence of injury which completely involves one of the branches of the bundle. Furthermore, to associate a wide QRS time with injury to the cardiac septum appears to be a justifiable deduction from the experimental observations. The effects on the QRS time which are toxic and are obtained by the exhibition of drugs like cocaine or quinine, or are endogenous (cardiac fatigue [2]), are not contrary evidence but represent a group of special conditions in which there is no distinction between conduction effects in the ordinary heart muscle and Purkinje tissues.

The tendency toward diminution in the QRS time from extensive destruction of the muscle in the presence of a bundle branch block suggests that initially it is the volume of the heart muscle in function and the thickness of the septum which determines the width of the QRS complex (when other conditions such as conduction changes do not alter it). Suggestive in this connection is the average width of the QRS time in the presence of a right bundle branch block in the cat, the dog and the human being. In the first, it is usually under 0.05 seconds, and in the dog it varies between 0.06 and 0.08 seconds,

18. Otto, H. L.: J. Lab. & Clin. Med., to be published.

whereas in man 0.12 seconds is the accepted minimum QRS time for bundle branch block. The abnormally wide QRS time in many greatly hypertrophied hearts may perhaps be explained in this way.

Since an altered position of the heart with reference to the leads as well as altered conduction order within the heart may cause notching, inferences from it concerning the muscle must be made with circumspection.

Finally, the term intraventricular block which is employed when an abnormal width of the QRS is present is more properly designated interventricular block. It represents a bundle branch block which, if partial, can be so only in a temporal sense, i.e., a delayed conduction through one branch of the bundle, not the effect of injury to some of its branchings. Intraventricular block should be the term reserved for instances in which a toxic prolongation of conduction diffused through the heart muscle is present.

SUMMARY AND CONCLUSIONS

1. Destruction of heart muscle causes a shift of the RT period of the electrocardiogram from the iso-electric line, and the degree to which this alteration occurs is closely related to the line of the leading as well as to the injury to the muscle.

2. The extensive destruction of heart muscle does not have a significant effect on the QRS complex of the electrocardiogram when the principal divisions of the His bundle are unaffected. An increase in the QRS time is obtained only when all of the bundle to one or the other ventricle is affected.

3. Arborization block represents a complex form of bundle branch block, involving all of the right branch and part of the left and associated with an altered position of the electrical axis with reference to the plane of the leading.

4. What is called intraventricular block is more properly termed interventricular, because the latter better defines the conditions of impulse conduction which underlie the appearance of this form of electrocardiogram.

CHRONIC PULMONARY INFECTION DUE TO THE FRIEDLÄNDER BACILLUS

A CLINICAL AND ROENTGENOLOGIC STUDY *

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Friedländer's pneumonia is an acute pulmonary infection, usually fatal, caused by *Bacillus mucosus-capsulatus* and characterized particularly by a viscid, bloody sputum and lobular involvement of the lung parenchyma with a marked tendency to the formation of secondary multiple abscesses.

In 1882, Friedländer described a "micrococcus" which he took to be the cause of lobar pneumonia. However, after Frankel and Weichselbaum had shown in 1886 that the pneumococcus was the causative organism in most cases of acute lobar pneumonia, it was found that the so-called "micrococcus" of Friedländer was in reality a short, gram-negative bacillus. This bacillus occurs either as a primary or a secondary invader in about 5 or 10 per cent of all cases of acute lobar pneumonia.

BACTERIOLOGY

The bacillus of Friedländer varies greatly in size and morphology. Usually it is short and rather broad, with rounded ends. Its length varies from 0.6 to 5 microns and its width from 0.5 to 1.5 microns. The short, thick forms are almost coccoid in appearance, which probably accounts for the fact that Friedländer originally called this organism a "micrococcus" rather than a bacillus. They are nonmotile, do not form spores and are surrounded by a capsule.

PATHOLOGY

There are certain outstanding features in the pathologic structure produced by the Friedländer bacillus. At autopsy the involved area appears to be lobar in type, but on section, multiple small intervening areas of normal lung tissue show that the process is, in reality, a marked confluent lobular pneumonia or bronchopneumonia. Pleurisy may be a prominent feature. Over the affected area, the visceral and

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parietal pleura may be densely adherent. The affected lung appears larger than normal, and when it is cut there is an abundant, viscid, bloody exudate. The cut surface is mahogany brown, with marble-like streaking. It is the rule for multiple abscesses to be found, these varying greatly in size. The walls of these abscesses are usually smooth and quite thin. In them is found the same type of exudate that is found on the cut surface of the lung. Between the cavities are seen irregular areas of air containing tissue. Relatively little fibrin is seen on the cut surface.

Microscopic examination shows the alveoli filled with an exudate composed of polymorphonuclear leukocytes, alveolar epithelium and degenerated lymphocytes. Some fibrin is seen, but it is much smaller in amount than that found in the pneumonia produced by the pneumococcus.

REVIEW OF THE LITERATURE

Concerning the clinical course of Friedländer's pneumonia, there is relatively little in the literature. In 1915, Sisson and Thompson[1] reviewed thirty-three fatal cases from the literature, some of which were open to question as unequivocal cases of Friedländer's pneumonia. They reported, in addition, four new cases, all of which were fatal.

In 1919, Zander[2] described an epidemic of Friedländer's pneumonia in Germany. Between December, 1916, and March, 1917, there were 411 cases with 144 deaths. The highest mortality occurred in the age groups of 30 to 40 and 40 to 50, being higher in the latter. In this epidemic, chills occurred at the onset in 118 cases, or 28 per cent. In the majority of the cases, the illness started in the lower lobes. In a large percentage of the cases the first examination showed that more than one lobe was involved. The extremes for the duration of fever were 2 and 48 days. The average was 9.5 days. In 131 cases (31 per cent) fever fell by crisis and in 127 (30 per cent) by lysis. In these cases the clinical observation was made that in the beginning, the picture was apt to be that of croupous pneumonia but later the picture became more that of bronchopneumonia.

Eighteen additional cases were reported by Belk,[3] of the Philadelphia General Hospital, in 1926, all of which had been fatal. Three of these cases had been considered chronic forms of pulmonary tuberculosis during life.

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1. Sisson and Thompson: Report of Thirty-seven Cases, Am. J. M. Sc. **150**:713, 1915.

2. Zander: Deutsche med. Wchnschr. **45**:1180, 1919.

3. Belk, W. P.: J. Infec. Dis. **38**:115 (Feb.) 1926.

An instructive case of Friedländer's pneumonia was reported by Nils Westermark [4] in 1926. His patient's illness started acutely with a chill which was followed two days later by pain in the left side of the chest. There were cyanosis, reddish sputum and bilateral physical signs in the chest. A diagnosis of bronchopneumonia was made. After a time the patient improved and was able to leave the hospital, but was readmitted six months later; at this time x-ray examination of the chest showed bilateral cavities in the upper lobes and changes in the lower lobes apparently due to fibrosis. The entire pathologic process was considered to be tuberculous, although tubercle bacilli had never been demonstrated. The patient died a month later. At necropsy multiple abscesses with rather a thin wall were found, and Friedländer's bacilli in great numbers were recovered from the contents of the cavities of the abscesses. Tubercle bacilli were not found. The record of one of our patients (case 2) resembles this case in several respects.

CLINICAL COURSE

The clinical course of Friedländer's pneumonia is variable. It occurs most frequently in the late years of adult life. Only one case, to date, has been reported during infancy or childhood. As in the case of acute lobar pneumonia, alcohol seems to be an outstanding predisposing factor. The onset may be similar to that of pneumococcic pneumonia. In fact, the case at first may be regarded as one of the usual lobar pneumonia. Hemoptysis is a common early symptom. The symptoms may come on with great violence accompanied by high fever, chill and prostration. Cyanosis may be a prominent symptom. The patient usually expectorates large amounts of viscid reddish sputum, and some writers regard this feature as being almost pathognomonic. In this sputum, the Friedländer bacilli are readily found in large numbers. In severe cases the prostration increases, the cyanosis becomes more marked and is combined with a dusky red coloration of the skin, and in the first twenty-four or forty-eight hours, death ensues.

On the other hand, the course of the disease may be quite prolonged or may become chronic. During the past year, we have had the opportunity of studying three such cases. It is our belief that cases of this kind give rise to a chronic form of Friedländer infection which we have come to regard as quite analogous to chronic pulmonary tuberculosis, as acute exacerbations may occur at any time. In our study of these cases we have been greatly aided by the roentgen-ray examination. By means of serial roentgenography, we have been able to follow the development of the pathologic condition from the onset of the disease to the establishment of the chronic stage.

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4. Westermark, N.: Pneumonia with Friedländer's Bacillus Simulating Tuberculosis; Case, Acta Radiol. **7**:626, 1926.

ROENTGEN-RAY ASPECTS

The literature concerning the roentgen-ray aspects of Friedländer's pneumonia is extremely meager. Our knowledge of the roentgenologic appearance is based on a study of the underlying pathologic condition. We recognize the onset of the disease as a bronchopneumonia, the roentgenologic features of which do not differ materially from bronchopneumonia due to other organisms. This stage of the disease is of such short duration that it is unlikely that many patients are examined by means of the roentgen ray during this period. Only one of our patients was examined this early in the disease (case 1).

The lobular patches of the primary bronchopneumonia coalesce rapidly to form larger areas which give the lung the appearance of lobar pneumonia. This differs from an ordinary pneumococcic lobar pneumonia in that the consolidation does not appear to be as complete and homogeneous and is not as definitely limited to a single lobe. The involvement is usually most intense in the periphery of the lung. Several such consolidations may be present in the same or the opposite lung. These characteristics have given rise to the condition being known as a pseudolobar pneumonia.

After a variable length of time, less rapidly in the nonfatal cases, extensive destruction of the tissue of the lung in the involved areas occurs, which lead to the formation of multiple abscesses and cavities. This gives rise to a characteristic roentgenographic appearance, which differs from all other acute pulmonary infections with the possible exception of influenza. A distinctive feature of these abscesses and cavities is their extremely thin walls to which attention was called by Belk and roentgenologically by Westermark.

It is in this stage that the disease usually terminates fatally. In those exceptional cases in which recovery occurs we have learned from our roentgenologic studies that the involved areas of the lung become the seat of an extensive fibrosis often with the persistence of cavities. We believe this residual fibrosis to be more or less permanent.

On the basis of this pathologic condition, we recognize roentgenologically four distinct stages of the disease. The first is the stage of primary bronchopneumonia, the second, the stage of pseudolobar pneumonia, the third, the stage of formation of multiple abscesses and cavities and the fourth, the stage of fibrosis.

REPORT OF CASES

CASE 1.—J. A., a slightly undernourished Italian, aged 50, was admitted to the service of Dr. Alfred Stengel in diabetic coma. The diabetes had been known to exist for three years, and during this time there had been lapses in the diabetic regimen, especially just before admission to the hospital. During the week before admission, he had spat up some dark red blood which he believed

came from the mouth. On admission, the blood sugar was 0.411 per hundred cubic centimeters and the plasma bicarbonate 13 per cent by volume. The chest was emphysematous in type but apparently was clear. The diagnosis was severe diabetic acidosis probably partially induced by some infection. The urine showed albumin varying from a trace to a cloud, and many casts of the hyaline, waxy, and light and dark granular variety. Four days after admission, the blood urea nitrogen was found to be 86 mg. per hundred cubic centimeters and during the next few days rose to 105 mg. Large doses of insulin were necessary to control the sugar level. Eight days after admission, facial cyanosis was distinct, and the patient complained of pain in the right side of the chest. Numerous frictions were heard in the right anterior axillary line at the level of the fourth rib. Posteriorly over the right lower lobe the percussion note was impaired and the breath sounds suppressed. It was thought that the patient probably had a low grade bronchopneumonia. A roentgenogram of the chest (fig. 1), taken the following day, was reported as suggesting a resolving pneumonia of the entire right lung.

For the following fourteen days, the general condition of the patient improved slightly. Fever continued, the temperature going as high as 100 F. The physical

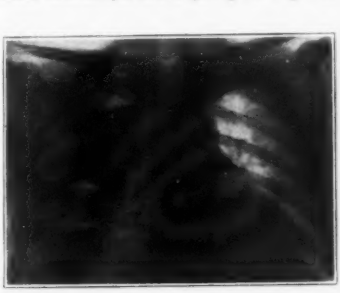

Fig. 1 (case 1).—Friedländer's pneumonia. The primary stage of bronchopneumonia.

signs in the chest came to involve a slightly greater area. X-ray examination at this time (fig. 2) showed that the pneumonic process had condensed into areas assuming a pseudolobar appearance. By this time, Friedländer bacilli began to appear in the sputum in large numbers both on smear and on culture. At this time the temperature varied between 99 and 101. Blood culture was entirely negative. Pneumococci or acid-fast organisms were not found on repeated examinations. The Wassermann reaction of the blood was negative.

Thirty-two days after admission, the physical signs in the right side of the chest remained practically unchanged, but x-ray examination (fig. 3) at this time showed multiple cavitation throughout the entire right lung. The sputum continued to show Friedländer's organisms in large numbers. During the next eight days the blood urea nitrogen had returned to normal, twenty-eight days having elapsed since it was 105 mg. per hundred cubic centimeters. Also during this time the blood sugar level became more definitely stabilized, ranging between 170 and 220 mg. per hundred cubic centimeters. From this time on there was no fever, although the improvement in the general condition of the patient was slight and extremely gradual. The physical and x-ray signs in the chest remained much the same except that the roentgenograms (fig. 4) showed that the cavities in the right lung were draining well. Friedländer's organisms con-

tinued to appear in the sputum. The patient now steadily improved and the diabetic situation was controlled in a satisfactory manner. He was discharged from the hospital 102 days after admission.

After he left the hospital, his general condition was good. Six months later he was admitted to the University Hospital, again for diabetic acidosis. On this admission, as on the previous one, he gave the history of having spat up blood

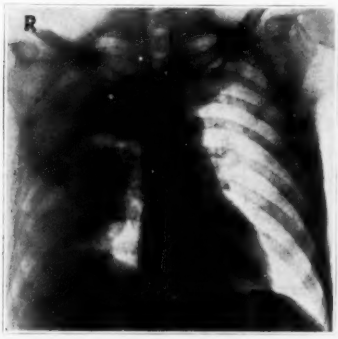

Figure 2

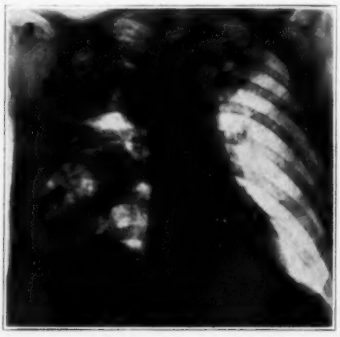

Figure 3

Fig. 2 (case 1).—The pseudolobar stage.

Fig. 3 (case 1).—The stage of multiple abscess and cavity formation.

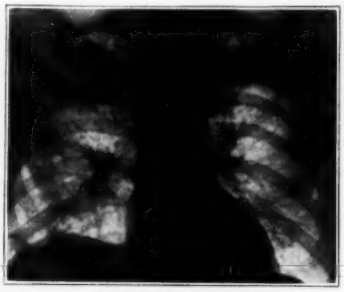

Figure 4

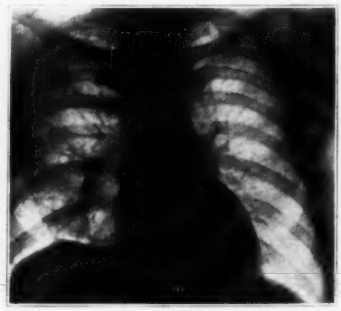

Figure 5

Fig. 4 (case 1).—The stage of fibrosis, showing the appearance of the lungs at the time of the patient's discharge from the hospital.

Fig. 5 (case 1).—Chronic stage, approximately ten and one-half months after the onset of the acute pneumonia.

a few days before admission. The diabetes was controlled more easily on this occasion. The striking aspect concerning the chest was that physical signs still remained over the right lung, and the roentgenograms (fig. 5) showed a diffuse scarring with lines marking the walls of the former abscess cavities.

CASE 2.—M. P., a thin white woman, aged 50, was admitted to the Hospital of the University of Pennsylvania, to the service of Dr. Alfred Stengel, on Feb. 9, 1927. Her chief complaint was cough and weakness. For a year previous to admission, she had complained of general weakness and a slight cough productive of a moderate amount of yellowish expectoration. However, her appetite had been good; she had not felt as if she had fever, and during the year she had lost only 3 pounds (1.4 Kg.). In August and in December, 1926, she had had grip, convalescence from the latter attack being slow.

On the morning of Jan. 30, 1927, she was awakened by an attack of coughing accompanied by a small amount of sputum tinged with bright red blood. The same thing occurred once on each of the two following days. On Feb. 4, 1927, she arose feeling weak and chilly, and was found to have a temperature of 102 F. The weakness, fever, cough and expectoration continued until she was admitted to the hospital. On February 6, she began to have pain, worse on deep breathing, in the lower portion of the left axilla, and this continued until she was admitted to the hospital.

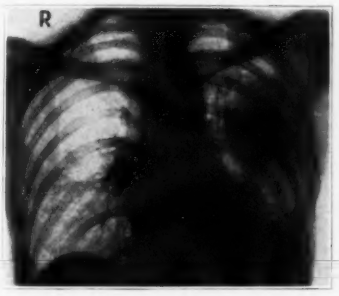

Figure 6

Figure 7

Fig. 6 (case 2).—The pseudolobar stage. Heart retracted to the left.

Fig. 7 (case 2).—Third stage. Large abscess in left upper lobe.

The past medical, the family and the social history did not have any bearing on the present illness.

On admission to the hospital, the temperature was 102 F.; the pulse rate, 120, and respirations, 32. The blood pressure was 140 systolic; 80, diastolic. The cheeks were flushed, but she lay quietly in bed and did not seem to be in pain. Examination of the chest revealed dulness to percussion in the left axilla with bronchovesicular breathing and many subcrepitant râles. Anteriorly, at the level of the third rib on the left side the percussion note was skodaic, and on auscultation the condition was the same as that in the left axilla. The tentative diagnosis was a partial consolidation of the left upper and left lower lobes. X-ray examination (fig. 6) suggested lobar pneumonia in the left upper and lower lobes with a retraction of the heart to the left. The leukocyte count was 12,700, with 84 per cent of polymorphonuclears. Organisms of the Friedländer type were present in the sputum. Tubercle bacilli were not found on repeated examination. The blood Wassermann reaction and blood culture were negative.

During the six days after admission, the temperature slowly returned to normal and the general condition of the patient steadily improved. During this

Figure 8

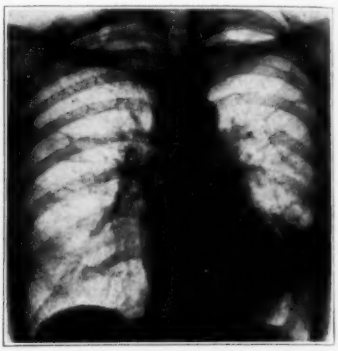

Figure 9

Fig. 8 (case 2).—Lateral view. Same as figure 7.

Fig. 9 (case 2).—Appearance of the lungs at the time of discharge from the hospital. It should be noted that the lesion in the left lower lobe had not changed and that the heart is still retracted to the left.

Figure 10

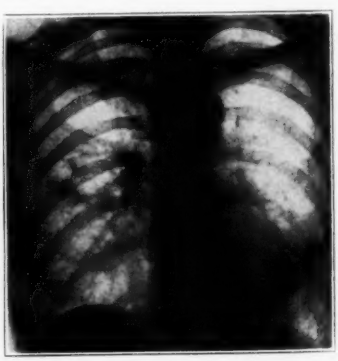

Figure 11

Fig. 10 (case 2).—Lateral view, same as figure 9, which best shows the large cavity in the left upper lobe with marked thickening of the interlobar pleura.

Fig. 11 (case 2).—Appearance six and one-half months after date of discharge. It should be noted how little change has occurred in that time.

time the left lung showed a tendency to clear, but after ten days the physical signs failed to improve. Three weeks after admission x-ray examination showed a large consolidation limited to the lower portion of the left upper lobe, and one week later this area had broken down with the formation of a large cavity (figs. 7 and 8). The roentgenograms of the chest showed that there was a fluid level in this cavity. The lesion in the left lower lobe had not changed. The temperature was normal, and the patient complained of nothing except moderate weakness. During this time, the Friedländer organism was recovered from the sputum repeatedly.

The patient steadily improved. An area of percussion dulness persisted at the left base, just to the left of the cardiac dulness, where there was some suppression of breath sounds and many subcrepitant râles. The temperature remained normal. Repeated x-ray examinations of the chest showed that the abscess in the left upper lobe apparently was draining well (figs. 9 and 10). The patient was discharged from the hospital on April 6.

During the summer of 1927, her general condition was good. One morning in July, just after arising she coughed up about a fourth of a cup of bright red

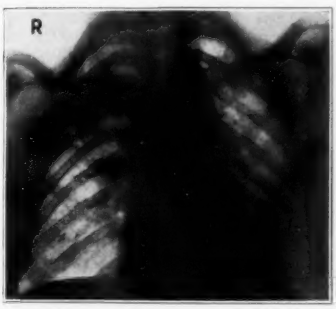

Figure 12

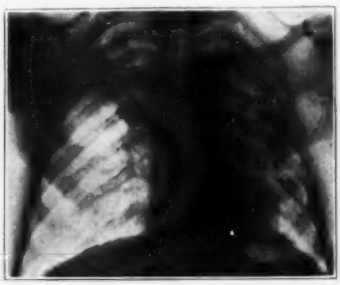

Figure 13

Fig. 12 (case 3).—Appearance of lungs on admission. Pseudolobar stage.

Fig. 13 (case 3).—Appearance approximately six weeks after admission, showing third stage in the left upper lobe and fourth stage in the right upper lobe.

blood. She had not had respiratory symptoms before this and had not been engaging in any unusual physical exertion. Further hemoptysis had not occurred. When this paper was written, she felt well. Physical examination still revealed signs at the left base. X-ray examination (fig. 11) showed a cavity still remaining in the region of the old abscess with fibrosis in the left base.

Case 3.—T. M., a well developed negro, aged 43, was admitted to the service of Dr. Alfred Stengel with the history and symptoms of acute lobar pneumonia. He had "caught cold" two weeks before admission, later developing pain in the right lower quadrant of the chest and yellowish sputum streaked with blood. During the past nine years, he had had five attacks of lobar pneumonia. In 1919 he had had a chancre for which he had been treated. The family and social history were irrelevant.

On admission to the hospital, the temperature was 103 F., the pulse rate, 124 and respirations, 40. The blood pressure was 70 systolic; 35, diastolic. Physical examination showed signs of consolidation over the right upper and the left lower lobes. The leukocyte count was 11,600. On culture the sputum showed

organisms of the Friedländer type and no pneumococci. Subsequently, Friedländer's organisms were isolated from the sputum repeatedly. Pneumococci or acid-fast bacilli were not found at any time. The blood Wassermann reaction and blood culture were negative.

During the first five days after admission the general condition of the patient improved; the temperature returned to normal by lysis, and the signs in the chest showed a tendency to improve. On the ninth day following admission, the patient became febrile and remained so for the following forty-five days. During a large part of this period, the temperature curve was septic in type. Chills and sweats were common. During this period, the patient became increasingly weaker. From the standpoint of physical examination, the outstanding symptom was the extreme indolence of the lesions in the lungs. The signs, at times, suggested a loculated or interlobar empyema. Repeated x-ray examinations of the chest tended to confirm this suspicion. Several attempts to locate fluid or pus with the exploratory needle failed. Finally, on the fifty-fourth day after admission, the temperature became normal and remained so. From this time on the patient made an uninterrupted recovery. At the time this paper was written, he was working in a brickyard and felt entirely well symptomatically.

The roentgenographic features of this case differed somewhat from those of the other two. On admission the appearance was that of consolidations involving the right upper and left lower lobes (fig. 12). Two weeks later there was considerable improvement in the lesion in the right upper lobe and no change in the left lower lobe. Two weeks later a reinfection had occurred in the right upper lobe which was even more extensive than the original involvement. A slight improvement was noted in the left lower lobe. Three weeks later it was found that the lesion in the right upper lobe had been replaced by a marked fibrosis and that the lesion in the left lower lobe had almost entirely disappeared. In addition, however, there was now a marked involvement of the left upper lobe which was undergoing formation of multiple abscesses and cavities (fig. 13). Ten days later the patient was discharged. A roentgenogram made at this time showed fibrosis of the right upper lobe with multiple abscesses in the left upper lobe. This case well illustrates the migratory nature of Friedländer's pneumonia.

COMMENT

We well realize the fact that the blood cultures were negative in these patients. However, to the best of our knowledge, all cases of Friedländer's pneumonia in which the organism has been recovered from the circulating blood have ended fatally. The repeated recovery of this organism in profuse growth from the sputum would point toward its being the etiologic agent. Our bacteriologic proof is not absolute but the other symptoms, clinical and roentgenographic, justify, we believe, the conclusion that the pulmonary lesions here described were produced by the Friedländer bacillus.

We believe, further, that the disease constitutes a distinct entity, one which can be and should be differentiated from other pulmonary infections. The acute form is most likely to be mistaken for bronchopneumonia or lobar pneumonia. Here one would have to rely on the clinical course, the bacteriologic and roentgenologic studies to make the

differentiation. Occasionally, one sees an influenzal pneumonia which may closely simulate Friedländer's pneumonia. The clinical course is often similar, and the disease may terminate with multiple cavitation and fibrosis. Aside from the absence of the Friedländer bacillus in such cases, we find roentgenologically that the principal involvement is in the tissues adjacent to the hilum, while in Friedländer's pneumonia the pathologic change is chiefly in the parenchyma of the lung.

Probably the most important aspect of Friedländer's pneumonia, particularly the chronic form, is its close resemblance to tuberculosis. So closely may these diseases simulate each other that in certain cases neither the clinical nor the roentgenologic evidence serves to make the differentiation. The diagnosis must rest on the bacteriologic examina-

Fig. 14.—Chronic Friedländer infection of the left lung.

tion alone. This has led us to the belief that undoubtedly many cases of chronic Friedländer infection are masking under the diagnosis of tuberculosis. A case in point has recently come to our attention.

A white man, aged 61, was admitted to the University Hospital (service of Dr. Alfred Stengel) because of symptoms in the stomach apparently due to pyloric carcinoma. He gave a history of cough and expectoration of long standing. The expectoration was a thick muco-purulent material. At the age of 41, or 20 years before admission, he had pneumonia. Since that time he had been told that he had "a bad left lung." Because of this, at one time he spent three months in a tuberculosis sanatorium, but the tubercle bacillus was never found in the sputum. Repeated examinations on this admission also gave negative results, but instead the Friedländer bacillus was recovered in large numbers. The x-ray examination (fig. 14) revealed a lesion involving the entire left lung with retraction of the heart and mediastinal structures toward the affected side. There was marked thickening of the pleura, extensive fibrosis and numerous cavities throughout the lung.

We believe that this pathologic condition dates back to the pneumonia that he had twenty years before admission, and that this case presents sufficient evidence to warrant the diagnosis of a chronic Friedländer infection of the left lung.

Case 2 of our series with the history of repeated attacks of grip, hemoptysis, cough and weakness might readily have led one to suspect tuberculosis. This case, we believe, was a chronic Friedländer infection with an acute exacerbation which caused the patient's admission in February, 1927. Our reasons for this conclusion are based on the history of the case plus the x-ray evidence of an old fibrosis of the left lower lobe causing a retraction of the heart to the left. The roentgenograms show that these symptoms were constant during the entire time the patient was under observation.

On the basis of our studies, we believe that Friedländer's pneumonia, particularly the chronic form, is far more common than is generally supposed. Its close resemblance to chronic pulmonary tuberculosis makes its recognition and differentiation important.

SUMMARY

1. Three cases of pneumonia due to the Friedländer bacillus are reported.

2. In two cases the onset suggested bronchopneumonia and in one lobar pneumonia.

3. The temperature fell by lysis in all cases, and in all the total leukocyte count tended to be lower than that seen in the usual case of lobar pneumonia.

4. The outstanding physical manifestation was the extreme indolence of the lesion of the chest.

5. There are characteristic x-ray symptoms which serve to differentiate this condition from other pulmonary infections.

6. Several months after the acute infection evidence of pathologic change can still be demonstrated both by physical and by x-ray examination.

7. From our studies we believe that there is a chronic form of pulmonary disease due to the Friedländer bacillus.

8. This chronic form is in many respects similar to chronic pulmonary tuberculosis. We therefore feel that in cases of suspected tuberculosis in which the organisms cannot be found the sputum should be examined for the Friedländer bacillus.

THE CHOLESTEROL CONTENT OF BLOOD PLASMA IN DIABETES MELLITUS

A STATISTICAL STUDY BASED ON TWO THOUSAND OBSERVATIONS IN THREE HUNDRED AND EIGHTY-FIVE CASES *

I. M. RABINOWITCH, M.D.
MONTREAL

Estimation of the cholesterol content of blood plasma is now part of the routine management of the diabetic patient in the Montreal General Hospital. Estimations are made at least on the admission of patients to the hospital and on their discharge and thereafter as regularly as possible, on their return to the clinic for the treatment for diabetes. All estimations are made on blood obtained from patients in the fasting state at least fifteen hours after the evening meal. Should patients require insulin, tests are made, as for blood sugar, not only before food is given, but before the administration of this drug. The present report is concerned with the study of 2,000 estimations made in 385 cases. All tests were made, not only under these standard conditions, but by the same technic and by the same laboratory workers. Patients observed for periods of less than six months are excluded from this study.

Plasma cholesterol is made use of as an index of lipoid metabolism in cases of diabetes mellitus for the following reasons: 1. It is a relatively stable chemical compound. 2. Its estimation is relatively simple. With reasonable care, no difficulties are encountered.[1] By the method employed,[2] recovery of added cholesterol is quantitative within the accepted limits of experimental error. 3. Plasma cholesterol values tend to run approximately parallel to those of the total fatty acids. Therefore, any changes of the latter are reflected in the former.

Interest in this phase of diabetes mellitus was first stimulated by the publications from Joslin's clinic and those of Professor Bloor.[3] These

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* From the Department of Metabolism, The Montreal General Hospital, Montreal.

1. Before applying the Lieberman-Burchard reaction in this test, colorimetric difficulties are entirely overcome if the alcohol-ether extract is allowed to evaporate to dryness for a period of hours in a drying oven at a constant temperature, rather than for a short period of time on a stove, as originally recommended by Bloor. By the former procedure, the development of the brownish color frequently encountered when the stove is used and which interferes with color reading, does not take place. The resulting solution is clear, and colors are easily matched.

2. Bloor, W. R.: J. Biol. Chem. **24**:227, 1916.

3. Joslin, E. P.; Bloor, W. R., and Gray, H.: The Blood Lipoids in Diabetes, J. A. M. A. **69**:375 (Aug. 4) 1917.

authors, by correlating their laboratory data with the various clinical types of diabetes, showed that "all types of diabetes are distinguished by a marked increase in the lipoids of the blood, and the general statement can be made that the increase is progressive with the seriousness of the disease." A rather important observation was that parallelism did not exist between the fluctuations in the blood sugar and lipoid, and that the amount of blood sugar present was not nearly as accurate a test of the severity of the disease as was the amount of blood lipoids. In a more detailed study, one of the workers of this group [4] again demonstrated a relationship between the lipoid content of the blood and prognosis. "The longer the duration of the disease before examination the lower the blood fat, presumably because those patients live long who have low fats, that is, mild diabetics." In his recent monograph, Joslin [5] briefly summarized the present knowledge of the physiology of the blood lipoids and in a striking manner further illustrated the prognostic value of their determination.

In a previous report of experiences with 254 subjects and a much lesser number of estimations than presently available, I [6] was able to confirm some of the observations made by Joslin and his co-workers. It was shown that the cholesterol content of the blood is a better index of the course of diabetes than the blood sugar. Patients may, on discharge from the hospital, have a normal amount of blood sugar and the urine may be free from sugar. In many of these cases, the cholesterol content of the blood is increased. By observing these patients as they return to the outdoor clinic, differences in progress are noted. The course of the patient who has a normal amount of blood sugar but a high cholesterol content does not, on the average, appear to run as uneventful for the same length of time as that of the patient who has not only a normal amount of blood sugar, but also a normal amount of cholesterol. When there is a large amount of cholesterol, the slightest dietary indiscretions result in more marked and more persistent hyperglycemia than when the cholesterol content is normal. Hyperglycemia resulting from slight illnesses appears to be more frequent with a large than with a normal amount of cholesterol, and when the cholesterol is increased, the incidence of neuritis and of vascular changes is greater. (Though neuritis, and even gangrene, may be observed in persons with a normal cholesterol content, the number of such cases is not sufficiently great to affect the rule.) The relationship between a large amount of cholesterol in the blood and

4. Gray, H.: Am. J. M. Sc. **168**:35, 1924.

5. Joslin, E. P.: Treatment of Diabetes, ed. 4, Philadelphia, Lea & Febiger, 1928.

6. Rabinowitch, I. M.: J. Canad. M. A. **17**:171, 1927.

gangrene is striking. Plasma cholesterol is also related to acidosis, though the relationship is not strictly quantitative.

The response of plasma cholesterol to treatment, either by diet alone or with insulin, differs not only with the severity of the disease, but with the type of the diabetic patient. The different types of curves obtained from data recorded at regular intervals appeared to be characteristic. In my experience, as will presently be shown, it is one of the best methods of estimating not only prognosis, but progress.

A few examples are cited:

A patient known to require insulin is discharged from the hospital. His urine is free from sugar and acetone bodies; the blood sugar is normal, and the plasma cholesterol is normal. He returns some time later to the clinic with a history of not having followed his diet and also of frequent appearances of sugar in the urine. The following are possible results in such cases: (*a*) blood sugar increased, plasma cholesterol normal; (*b*) blood sugar increased, plasma cholesterol increased.

In the former case, diet alone is usually sufficient to reduce the blood sugar to the normal level. The blood sugar usually falls rapidly. In spite of dietary indiscretions, carbohydrate tolerance apparently has not been impaired. The urine can still be kept free from sugar and acetone bodies and the blood sugar normal on a diet compatible with normal requirements.

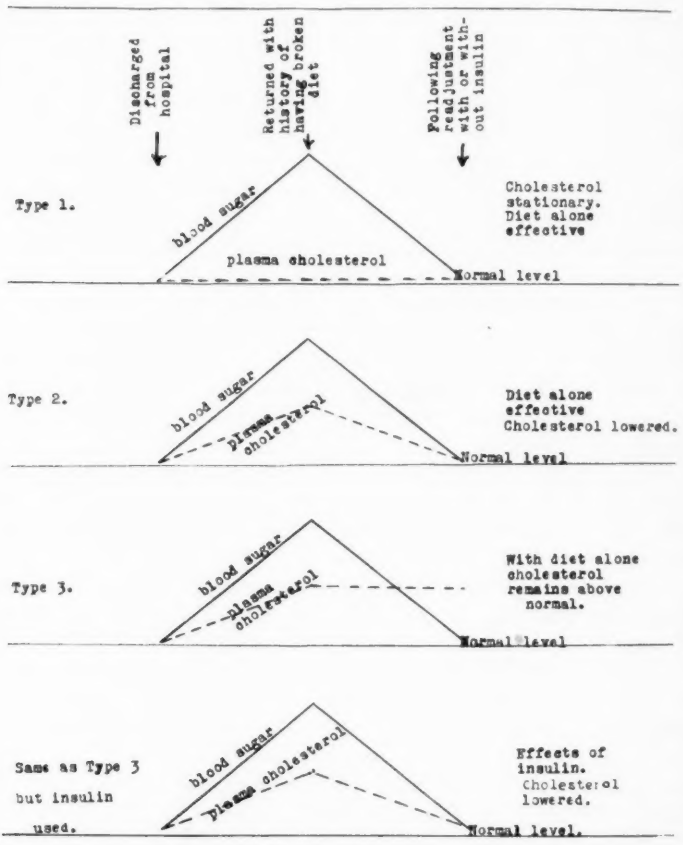
When, however, besides a hyperglycemia, hypercholesterolemia is also present, the blood sugar may not return to the normal level after restriction of diet alone; if it does, it does so much more slowly than when the cholesterol content is normal.

The cholesterol itself may or may not return to the normal level after readjustment of diet. Should it not return to the normal level, insulin is usually found necessary to maintain ideal conditions; namely, a normal blood sugar and urine free from sugar and acetone bodies when the patient's diet is compatible with the requirements. The possible results are diagrammatically recorded in the accompanying chart.

Since it is possible to decrease the cholesterol content of blood plasma, either by regulation of the diet alone or by such regulation plus insulin, the values found when patients are first seen, that is, prior to treatment, have limited significance in the estimation of progress. Two extreme examples are cited in table 1 to demonstrate how rapidly reductions may take place following the use of insulin. On admission to the hospital, both patients had severe acidosis.

The following are examples of reductions of cholesterol following treatment of patients with a less severe form of diabetes, that is, patients with glycosuria and hyperglycemia, but without acetonuria. One of these patients (W. S. F.) did not require insulin, and the other patient (Case No. 13818/26) did.

Persons with diabetes, in whom the disease is complicated by infection, may, as is well known, fail to respond even to massive doses of insulin. The plasma cholesterol is particularly of value here. Since there is a relationship between lipemia and acidosis, data on cholesterol tend to indicate the degree of susceptibility of such patients to this



Diagrammatic representation of the relationship between plasma cholesterol and progress of patients who do not follow diets.

complication. The following is an example: The patient (#1002127) was admitted to the hospital with diabetes complicated by pneumonia. At the time of admission, the urine contained a large amount of sugar, but no acetone bodies. During the febrile state, the reaction to insulin was practically nil. Marked glycosuria persisted. Acetonuria was not

present. The plasma cholesterol was below the normal average, namely, 0.145 per cent. The prognosis therefore appeared to be good. The patient recovered. Following the crisis, the urine became sugar-free and remained so without the use of insulin. On discharge from the hospital, the patient was, and still is, on a diet consisting, approximately, of 150 Gm. of carbohydrates.

Carotinemia and cholesterolemia appear to be related. This combination of conditions was previously reported.[7] Interpretation of cholesterol

TABLE 1.—*Rapid Reduction of Cholesterol Content in Two Cases of Severe Diabetes*

Case 5728/28		Case 5517/28	
Date	Cholesterol, per Cent	Date	Cholesterol, per Cent
Oct. 7, 1928	1.380	Sept. 28, 1928	0.925
Oct. 8, 1928	0.980	Oct. 1, 1928	0.596
Oct. 9, 1928	0.640	Oct. 11, 1928	0.406
Oct. 10, 1928	0.520		

TABLE 2.—*Reduction of Cholesterol in Less Severe Cases of Diabetes*

W. S. F.		Case 13818/26	
Date	Cholesterol, per Cent	Date	Cholesterol, per Cent
Jan. 7, 1927	0.400	Dec. 14, 1926	0.401
Jan. 28, 1927	0.292	April 12, 1927	0.222
March 8, 1927	0.223	May 21, 1927	0.229
July 15, 1927	0.212		

TABLE 3.—*Cholesterol Data in a Case of Carotinemia and Cholesterolemia*

Case 6049/27	
Date	Cholesterol, per Cent
Nov. 23, 1927	0.456
Nov. 26, 1927	0.347
March 1, 1928	0.476
May 1, 1928	0.709
Aug. 29, 1928	0.512

data in such cases is difficult. Since vegetables are known to contain cholesterol-like bodies, limited significance must be attached to the observations in these cases, except that carotinemia, by itself, suggests unfavorable prognosis. Table 3 shows the cholesterol data in such a case. The patient died recently of a cerebral hemorrhage.

It is remarkable that in spite of patients' persistent disregard of dietary regulations, and although they have persistent glycosuria, the plasma cholesterols may remain within the normal limits. The prog-

7. Rabinowitch, I. M.: J Canad. M. A. **18**:527, 1928.

nostic significance of cholesterol in these cases is suggested from the fact that such patients appear to make good progress in spite of the misleading laboratory data. Such cases, however, are few.

The reverse of this picture is shown in the type of case in which the amount of cholesterol increases in spite of the fact that the patient follows the prescribed diet rigidly. The number of these cases also is few. An example is shown in table 5.

TABLE 4.—*Cholesterol Data in a Case in Which Diet Is Disregarded*

	Case 3388/27
Date	Cholesterol, per Cent
June 30, 1927	0.197
July 4, 1927	0.192
July 9, 1927	0.197
July 25, 1927	0.179
Aug. 5, 1927	0.188
Feb. 23, 1928	0.166
May 1, 1928	0.191

TABLE 5.—*Cholesterol Data in a Case in Which Diet Is Followed*

	Metabolism Laboratory 160
Date	Cholesterol, per Cent
April 1, 1927	0.191
June 2, 1927	0.190
July 7, 1927	0.185
Sept. 30, 1927	0.192
March 24, 1928	0.277
May 5, 1928	0.350

TABLE 6.—*Case in Which Synthalin Was Used*

Date	Plasma Cholesterol, per Cent	Remarks
April 19	0.219	Before treatment
April 22	0.180	Three days after treatment
May 13	0.204	
June 9	0.181	
July 9	0.158	
July 15	.....	Insulin replaced by synthalin
July 25	0.222	
August 5	0.205	
September 19	0.245	
October 17	0.303	

Synthalin, unlike insulin, apparently fails to control cholesterolemia. This was shown in a previous report.[8] The patient requires insulin, but the diabetes has been kept under control with synthalin for the past fifteen months. The results in another case in which the patient requires insulin and has been receiving synthalin since August, 1927, are given in table 6.

8. Rabinowitch, I. M.: An Unusual Case of Diabetes and Gout, J. Canad. M. A. **21**:682, 1928.

It will be noted that the cholesterol values are distinctly higher and are increasing since the use of insulin was discontinued.

An objection which may be raised to these observations is that the few cases cited may be exceptions rather than the rule, and that a study of average values of a large series of cases would be of greater value. Fortunately, the number of patients who have been observed and the cholesterol estimations which have been made are large and sufficient

TABLE 7.—*Plasma Cholesterols and Their Incidences Based on Two Thousand Observations*

Plasma Cholesterol, per Cent	Incidence
175	334
176 - 200	246
201 - 225	272
226 - 250	296
251 - 275	224
276 - 300	218
301 - 325	104
326 - 350	106
351 - 375	50
376 - 400	34
401 - 500	76
500 +	40

TABLE 8.—*Subjects Grouped According to Laboratory Data*

Group	Laboratory Data
1	Urine sugar-free; blood sugar normal
2	Urine sugar-free; blood sugar less than 0.18 per cent
3	Glycosuria once a month
4	Glycosuria twice a month
5	Glycosuria once a week
6	Glycosuria twice a week
7	Glycosuria daily, but free at times
8	Glycosuria persistent

TABLE 9.—*Average Cholesterol Values for Subjects in Table 8*

Group	Choltesterol, per Cent
1	0.184
2	0.209
3	0.230
4	0.252
5	0.272
6	0.288
7	0.320
8	0.379

to enable statistical treatment of the data. The results of such treatment are given in table 7; they appear to demonstrate definitely the value of plasma cholesterol from the point of view of progress.

In table 7 are shown plasma cholesterols and their incidence in 2,000 instances.

In order to determine whether or not the cholesterol content of the blood plasma is related to the degree of control of the disease, all subjects were grouped according to the laboratory data, as shown in table 8.

The average cholesterol values were calculated for each group. The results are shown in table 9.

The question which arises is, Are the differences between the averages of the various groups significant? In order to attempt to answer this question, the following values were calculated for each of the groups mentioned: (*a*) number of cases, (*b*) average percentage of cholesterol, (*c*) standard deviation and (*d*) probable error of the mean. These are recorded in table 10.

With this information, it is possible to determine whether the differences observed between the means of any two groups one wishes to

TABLE 10.—*Showing Arithmetical Means, Standard Deviations and Probable Errors of the Means of Plasma Cholesterol Percentages Grouped According to the Degree of Control of Diabetes*

Group	Number of of Observations (N)	Arithmetical Mean (A. M.)	Standard Deviation (σ)	Probable Error of Mean $\left(0.67449 \frac{\sigma}{\sqrt{N}}\right)$
1. Urine sugar-free: blood sugar normal	314	0.184	57.1	3.1
2. Urine sugar-free: blood sugar less than 0.180 per cent.	332	0.209	61.0	3.3
3. Glycosuria once a month	400	0.230	52.1	2.6
4. Glycosuria twice a month	260	0.252	59.8	3.5
5. Glycosuria once a week	246	0.272	63.6	3.8
6. Glycosuria twice a week	220	0.288	80.8	5.2
7. Glycosuria daily, but free at times	182	0.320	91.1	6.4
8. Glycosuria persistent	46	0.379	171.1	15.8

TABLE 11.—*Showing Differences Between Means, the Probable Errors of the Differences and the Ratios of the Differences to the Probable Errors of the Differences*

Groups Compared	Difference Between Means	Probable Error of Difference*	Difference / Probable Error of Difference
1 and 2	25	4.5	5.5
2 and 3	21	4.2	5.0
3 and 4	22	4.3	5.1
4 and 5	20	5.1	3.9
5 and 6	16	6.4	2.5
6 and 7	32	8.2	3.9
7 and 8	59	17.1	3.4

* If p_1 is the probable error of the mean of group 1, and p_2 is the probable error of the mean of group 2, then $\sqrt{(p_1)^2 + (p_2)^2}$ is the probable error of the difference.

compare are due to the control of the diabetes or the result of chance. Comparisons were made between the following groups: 1 and 2, 2 and 3, 3 and 4, 4 and 5, 5 and 6, 6 and 7 and 7 and 8. The necessary calculations were as follows: (*a*) the differences between the means, (*b*) the probable errors of the differences and (*c*) the ratios of the differences between the means to the probable errors of the differences. The results of these calculations are shown in table 11.

In each case, it is clearly demonstrated that the occurrence of the differences between the means of the groups compared were not the result of chance. The significance of the difference between the

average amounts of cholesterol of groups 5 and 6 is the only one in doubt. Even here, however, it may be shown that the odds against the occurrence of such a difference between the cholesterol content being the result of chance are about 10 to 1.

CONCLUSIONS

Plasma cholesterol affords a reliable index to the true progress of the diabetic patient.

Because of the simplicity with which the test can be carried out, estimation of the plasma cholesterol should form part of the routine management in diabetes.

As with all laboratory tests, in the interpretation of results obtained consideration should be given to other conditions which might lead to high values. These include jaundice, cholecystitis, pregnancy, nephrosis, etc.

THE CHOLESTEROL CONTENT OF BLOOD PLASMA IN JUVENILE DIABETES

A STATISTICAL STUDY *

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In a previous report [1] I demonstrated the value of cholesterol studies in diabetes from the point of view of progress. The demonstration, with the exception of a few cases cited as examples, was statistical. The data concerned adults only, since, as is well known, the diabetes of juveniles differs in many respects from that of adults. The report was based on 2,000 observations in 385 cases.

This brief report is concerned with the study of the cholesterol content of blood plasma in cases of juvenile diabetes. The various reasons for making use of plasma cholesterol as an index of lipoid metabolism in diabetes were discussed in the first paper and, for purposes of brevity, are omitted here.

The literature on this phase of juvenile diabetes is scanty. There are various reasons for this. In the first place, the material available in any one clinic is relatively small, since juveniles represent only about 5 per cent of the total number of all diabetic patients. Another reason is that, judging from literature, lipoid metabolism studies do not, except in a few clinics, form part of the routine management of diabetes. Joslin recorded his experience with twenty-six children. In one group of twenty-one cases the maximum, minimum and average cholesterol values were 0.109, 0.226 and 0.146 per cent, respectively, and in five cases of another group the corresponding values were 0.312, 0.500 and 0.385 per cent. Because of the limited material available at the time, Joslin hesitated to venture to interpret these values. It is obvious, therefore, that with the accumulation of more data, more will be known of this phase of diabetes, and it is for this reason that I wish to add to the literature my experience with this phase of the disease.

Forty-six children were studied.[1] This investigation was made along the same lines as that concerning diabetes in adults previously reported, that is, an attempt was made to determine, statistically, whether in juvenile diabetes plasma cholesterol is related to, and can afford an idex of, progress. In order to determine the latter, the following studies were made: (*a*) a comparison between plasma choles-

* Submitted for publication, Dec. 12, 1928.

* From the Department of Metabolism, The Montreal General Hospital, and the Henry J. Elliott Laboratory of the Shriners' Hospital, Montreal.

1. Rabinowitch, I. M.: The Cholesterol Content of Blood Plasma in Diabetes, Arch. Int. Med., to be published.

terol of diabetic and nondiabetic children; (*b*) the relationship between cholesterol content of blood plasma and degree of control of diabetes, and (*c*) the relationship between cholesterol content of blood plasma and insulin dosage.

Estimations were made on specimens of blood of forty-four normal children [2] under the same standard condition as previously described. Their ages ranged from 3½ to 14 years. Both sexes were fairly equally represented. There were twenty-three boys and twenty-one girls. Table 1 gives a brief summary of all of the analyses of the blood of both diabetic and nondiabetic patients.

TABLE 1.—*Blood Analyses of Diabetic and Nondiabetic Patients*

Subjects	Cholesterol, per Cent		
	Maximum	Minimum	Average
Nondiabetic	0.234	0.111	0.176
Diabetic	0.600	0.120	0.243

TABLE 2.—*Subjects Grouped According to Laboratory Data*

Group	Laboratory Data
1	Urine sugar-free; blood sugar normal
2	Urine sugar-free; blood sugar less than 0.18 per cent
3	Glycosuria once a month
4	Glycosuria twice a month
5	Glycosuria once a week
6	Glycosuria twice a week
7	Glycosuria daily, but free at times
8	Glycosuria persistent

As in the case of the adults studied in the attempt to determine whether there was any relationship between plasma cholesterol and the control of the diabetics, the subjects were grouped according to the laboratory data as in table 2.

Though this classification may appear arbitrary, it has, in my experience, been found practical. The average plasma cholesterol values were then calculated for each group. The results are shown in table 3.

TABLE 3.—*Cholesterol Values for Groups in Table 2*

Group	Number of Cases	Average Plasma Cholesterol, per Cent
1	10	0.176
2	8	0.224
3	5	0.220
4	6	0.286
5	1	0.260
6	3	0.264
7	6	0.236
8	7	0.350

2. This material was made available at the Shriners' Hospital for Crippled Children of Montreal. All of these children were normal with the exception of having congenital, or acquired, bone deformities (clubfeet, etc.).

It is obvious that, because of the small number of patients in each group, limited significance must be attached to the average values found. In order, therefore, to treat the data statistically, the numbers were increased by dividing all subjects into two groups, namely: (*a*) those who had glycosuria and (*b*) those whose urines were sugar free.

Twenty belonged to the former and twenty-six to the latter group. The following values of each group were then determined: (*a*) arithmetical mean (average cholesterol), (*b*) standard deviation, (*c*) probable error of the mean. From these values were then calculated:

TABLE 4.—*Statistical Demonstration of the Relationship Between Control of Blood and Urine Sugar and Plasma Cholesterol*

Group	Number of Cases (N)	Average Cholesterol (M) per Cent	Standard Deviation (σ)	Probable Error of Mean†	Probable Error of Difference Between Means*	Difference Between Means / Probable Error of Difference
1. No glycosuria	20	0.184	37.4	5.6	14.8	6.9
2. Glycosuria	26	0.285	103.9	13.7		

† $0.67449 \frac{\sigma}{\sqrt{N}}$ * $\sqrt{(5.6)^2 + (13.7)^2}$

(*a*) the difference between the means and (*b*) the ratio of the difference between the means to the probable error of the difference. The results of these calculations are shown in table 4. It will be seen that the ratio of difference between the means to the probable error of the difference was 6.9. The latter figure makes it practically certain that the difference between the average amount of cholesterol of the two groups is the result of the degree of control of the diabetes and not the result of chance. In other words, children with glycosuria, that is, those in whom the diabetes is not controlled, tend to have a high cholesterol content of the blood.

Further proof of this conclusion was sought from another point of view. An attempt was made to determine whether there was any relationship between plasma cholesterol and insulin dosage. For this purpose all children were divided into four groups: (*a*) those for whom it has been necessary to increase the dosages of insulin; (*b*) those for whom the amounts required when first seen have remained unchanged; (*c*) those who were able to take decreased amounts, and (d) those who were able to discontinue its use entirely.

Table 5 shows the average values of plasma cholesterol of the different groups.

Again, the number of cases corresponding to each group was small, and in order to treat the data statistically, the children were divided

into two large groups, namely: (*a*) those who were able to take a decreased dosage of insulin, and (*b*) those who were not able to do so. In each case, the same calculations were made. The results are recorded in table 6.

It will be seen that the ratio of the difference between the means to the probable error of the difference was 4.7. The odds against the occurrence of such a difference as found between the means, being the result of chance, were, therefore, about 650 to 1. In other words, it is certain that insulin dosage was related to the plasma cholesterol.

From the results obtained in these studies, it appears that the plasma cholesterol of juvenile diabetic patients affords the same index of

TABLE 5.—*Average Plasma Cholesterol Values*

Group	Number of Cases	Average Plasma Cholesterol, per Cent
1.	19	0.200
2.	7	0.224
3.	13	0.226
4.	7	0.185

TABLE 6.—*Statistical Demonstration of the Relationship Between Insulin Dosage and Plasma Cholesterol*

Group	Number of Cases (N)	Average Cholesterol (M) per Cent	Standard Deviation (σ)	Probable Error of Mean†	Probable Error of Difference Between Means*	Difference Between Means / Probable Error of Difference
1. Able to decrease insulin	20	0.200	47.5	7.1	16.2	4.7
2. Unable to decrease insulin	26	0.277	110.5	14.6		

† $0.67449 \frac{\sigma}{\sqrt{N}}$ * $\sqrt{(7.1)^2 + (14.6)^2}$

progress for the child as it does for adults. In view, however, of the small number of observations, these results are reported not because I am convinced that they would apply to a larger series of persons, but in order that others, with similarly available data, may test the conclusion. As has been stated, in view of the low incidence of juvenile diabetes, the material available in any one clinic is small.

It is of interest here to note that in a study of the blood fat of diabetic children, Gladys Boyd [3] reached a somewhat similar conclusion, namely: "Increasing tolerance indicating a more or less constantly normal blood sugar usually results in maintenance of the blood fat at the normal level . . ."

3. Boyd, G. L.: Blood Fat in Diabetic Children, Am. J. Dis. Child. **36:** 298 (Aug.) 1928.

DIABETES MELLITUS

A STUDY OF ONE HUNDRED AND FORTY-SEVEN AUTOPSIES *

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The present study is composed of an investigation of about 170 cases of diabetes mellitus in which autopsy had been performed. It was hoped that some correlation might be made of the clinical and pathologic observations. For this purpose we studied the clinical record, the protocol of the autopsy and the microscopic sections. From Dr. von Glahn of the Presbyterian Hospital we obtained forty-nine cases, from Dr. Rich of the Johns Hopkins Hospital thirty-six cases, from Dr. Symmers of Bellevue Hospital twenty-five cases, from Dr. Gross of Mount Sinai Hospital seventeen cases, from Dr. Rohdenburg of the Lenox Hill Hospital eight cases, from Dr. Denton of the New York Hospital eight cases and from Dr. MacNeal of the Post-Graduate Hospital four cases. These cases date from 1909 to 1926, inclusively, and are therefore not duplicates of the series reported by Cecil.[1] In only 147 of the 170 cases reviewed did we obtain sufficient data for our purpose.

CLINICAL DATA

Age Incidence, Sex, Color and Nativity.—The ages ranged from 12 to 76 years. The distribution as to decades is given in table 1. Seventy-two of the patients were females and seventy-five males. There were 132 Caucasians, fourteen negroes and one Chinese. The native born patients numbered ninety-one, the Jewish, fifteen; the others were divided in groups of one to three between the countries of Europe.

Family History.—Five cases presented a distinct history of diabetes in one or more members of the immediate family.

Duration of Symptoms.—Twenty-two patients had had symptoms of diabetes for more than five years, thirty-six for more than one year, twenty-nine for more than six months, eighteen for less than six months, while nine had not had symptoms and the condition was discovered by the usual routine tests of the hospital. For the remaining eighteen cases there appeared no information in the history to indicate that the patient had been questioned as to the length of his illness. One

* Submitted for publication, Dec. 6, 1928.

* From the Department of Pathology of Cornell University Medical College.

1. Cecil, R. L.: Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med. **11**:266, 1909.

patient had been under observation for twenty-five years because of diabetes.

Insulin.—Since the majority of patients died before the general use of insulin, we have not considered this factor in our statistics.

GROSS AND MICROSCOPIC EXAMINATIONS OF PANCREAS

The description of the appearance and weight of the pancreas was neglected in many cases, and even when the weight is given one suspects the inclusion of extraneous fat and blood vessels. We have not tabulated these figures for this reason.

In every case the usual sections were stained with hematoxylin-eosin, and in almost all cases more than two portions of the organ were sectioned.

TABLE 1.—*Age Distribution According to Decades in Patients with Diabetes*

		Interstitial Pancreatitis		Lipomatosis		Arteriosclerosis	
Age	Cases	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
10 to 20	12	1	8	0	0	1	8
21 to 30	15	4	26.6	0	0	1	6.5
31 to 40	16	7	44	1	6.3	2	12.5
41 to 50	36	23	64	8	22	12	33.3
51 to 60	45	29	64	20	44.4	29	64
61 to 80	23	15	66	12	52	18	78

ASSOCIATED LESIONS OF OTHER ORGANS

Endocrine Disorders.—Nine patients had adenomatous thyroids and one, colloid goiter. One showed hypoplasia of the suprarenals, another showed hyperplasia, while a third had fatty infiltration of the suprarenal cortex. Three cases were classed as status lymphaticus.

Lesions of the Liver.—Of seven of the fifteen patients having cirrhosis of the liver, the condition was associated with hemochromatosis and one had a hepar lobatum. All but two of these showed interstitial pancreatitis. Adami [2] referred to the frequent association of these two conditions. Sixty-seven showed some fatty change, and of these forty had definite fatty infiltration.

Lesions of the Heart.—Root and Warren [3] were particularly impressed by the early occurrence of myocardial damage in diabetic patients. In their series of twenty-six patients, there were five under the age of 40 who showed coronary sclerosis, chronic myocarditis or coronary thrombosis. Sclerosis of the coronary vessels occurred in

2. Adami and McCrae: A Textbook of Pathology, Philadelphia, Lea & Febiger, 1912, p. 595.

3. Root, H. F., and Warren, S.: Clinical Pathology of Twenty-Six Cases of Diabetes, Boston M. & S. J. **45**:194, 1926.

twenty of our patients, but only one of them was under 40. Infarction of the ventricular muscle occurred in eleven patients, all of them over 40 years of age, while chronic myocarditis was present in nineteen over 40 and in one under 40. No relation was found between the degree of myocardial damage and that of the islands of Langerhans. In the group showing hemochromatosis, 43 per cent were affected with chronic myocarditis, but the factors producing the change here were obviously other than diabetic.

Acute Infections.—Thirty-seven patients had suppurative lesions. Twelve had multiple abscesses, twelve cellulitis, eight perinephritic abscesses, two carbuncle and three otitis media. A surprising number showed ascending infections of the urinary tract; these numbered twenty-one, or 14.5 per cent. Thirty-six cases gave evidence of pneumonic involvement at autopsy.

LESIONS OF THE PANCREAS

Interstitial Pancreatitis.—Interstitial pancreatitis was present in 123 cases, of which ninety-five or 64.8 per cent, showed interacinar, and twenty-eight or 19 per cent, interlobular, fibrosis. Cecil [1] found that 71 per cent of his cases showed interacinar, and 4.4 per cent, interlobular, fibrosis. If one disregards those cases in which only a slight increase in fibrous tissue occurred, there remain seventy-nine, or 53.7 per cent, of all our cases which showed a well developed interstitial pancreatitis. Table 1 gives the age incidence in interstitial pancreatitis and shows that, while this lesion is seen to increase with age, the high proportion of persons affected in middle life must be explained by some other factor. One that suggests itself is acute inflammation of the parenchyma, which heals by fibrosis. Six cases in the series bear out this theory.

Case 121.—The patient, aged 44, showed a pancreas which was the seat of a single large abscess surrounded by a thick fibrous wall. This had apparently been due to a perforated peptic ulcer. The onset of the diabetes occurred seven weeks prior to death.

Case 47.—A man, aged 54, was found to have an elongated abscess under the peritoneum in contact with the pancreas. He had been admitted to the hospital for cirrhosis of the liver with ascites, and gave no history of diabetic symptoms.

Case 36.—A man, aged 26, showed hemorrhage into the substance of the pancreas with leukocytes infiltrating the connective tissue. He gave a history of four weeks' duration of diabetic symptoms.

Case 51.—A man, aged 23, showed necrosis of the head of the pancreas with healing productive fibrosis. His symptoms had lasted two years.

Case 90.—A man, aged 75, showed hemorrhage into the fat and septums of the pancreas, with polymorphonuclear leukocytes in the extravasated blood. His symptoms had increased markedly in the six weeks prior to his death.

Case 116.—A man, aged 62, showed marked edema of the fibrous tissue of the pancreas, which was invaded by wandering cells. He had been admitted for an infected hand and had not had symptoms of diabetes until admission.

These cases suggest that a possible etiology of the chronic productive fibrosis seen at autopsy may be the result of acute infections, and, further, that these acute inflammations may account for the sudden onset in certain cases of diabetes.

Another cause of interstitial pancreatitis may be sought in its relation to gall bladder disease. Eleven patients of the series had chronic cholecystitis, and all but one had definite fibrosis of the pancreas. In ten cases stones were found in the gallbladder without evidence of cholecystitis; of these, six showed interstitial pancreatitis. In case 14a, the pancreas was represented by a long strand of fibrous tissue in which were embedded fairly numerous islands. It seems probable that at one time there had been an occlusion of the duct, and since a pancreatic

TABLE 2.—*Effect of Interstitial Fibrosis on Island Cells* *

Island Lesion	Total Cases	Interstitial Pancreatitis		Capsular Thickening	
		Cases	Per Cent	Cases	Per Cent
Normal islands	11	3	28	3	27
Pyknotic islands	15	7	46	3	20
Slight fibrosis	31	14	45	17	55
Moderate fibrosis	23	11	48	16	70
Marked fibrosis	25	16	64	16	64
Hyaline islands	30	22	73	16	58
Hemachromatosis	7	7	100	4	57

* Classification of Lesions of Islands of Langerhans
I. Normal islands
II. Fibrosis of islands
(a) Slight fibrosis
(b) Moderate fibrosis
(c) Marked fibrosis
III. Hyaline degeneration
IV. Pyknotic changes
V. Hemochromatosis
VI. Capsular thickening
VII. Hemorrhage into the islands
VIII. Giant nuclei

calculus was not found at autopsy, it may well have been caused by a stone in the ampulla. The organ resembled those described by MacCallum [4] after experimental ligation of the duct.

The effect of interstitial fibrosis on the island cells is definitely shown in table 2; that is, the more serious the damage to the islet, the greater is the percentage of interstitial change. Severe interacinar fibrosis results in atrophy of the parenchymatous tissue. This may account for the clinical observations of Jones, Castle, Mulholland and Bailey [5] who reported a series of diabetic cases; half of these showed diminished activity of the pancreatic secretions.

Lipomatosis.—It seems possible that the atrophied tissue of the pancreas is replaced by fat. Lipomatosis of the pancreas is practically

4. MacCallum, W. G.: Relation of the Islands of Langerhans to Glycosuria, Bull. Johns Hopkins Hosp. **20**:265, 1909.

5. Jones, C. M.; Castle, W. B.; Mulholland, H. B., and Bailey, F.: Pancreatic and Hepatic Activity in Diabetes Mellitus, Arch. Int. Med. **35**:315 (March) 1925.

absent among patients under 40 years of age. Half of the patients over 60 are affected (table 1). Its incidence follows that of interstitial pancreatitis by about twenty years. In extreme cases the islands are isolated from the acini by areolar tissue.

Tuberculosis.—Tuberculous lesions of the pancreas were not found in any case.

LESIONS OF THE ISLANDS OF LANGERHANS

Since serial sections were not available, figures of the number or size of the islands found in any case are not given. Adenomas of the insular tissue were not seen. While certain of the islands seemed larger than others, we are not able to present any observations that would substantiate the theories of regeneration and hypertrophy.

Capsular Thickening.—Capsular thickening was present in 53 per cent of all cases. According to Otani,[6] there is no capsule for the normal island beyond the basement membrane of the surrounding acini. He regarded the capsule as a definite indication of interstitial inflammation. Other observers stated that the normal island is surrounded by a delicate connective tissue framework, one or more cells of which can be seen on section and which sends delicate strands into the island; these act as a support for the islet cells and carry the blood vessels and nerves. Capsular thickening occurred in conjunction with interstitial pancreatitis in 61 per cent of the cases. It appears to be more closely related to fibrosis of the islands, since in the normal and pyknotic group it was present in less than 30 per cent of the cases, while in the fibrotic groups it ranged from 55 to 70 per cent (table 2).

Normal Islands.—In eleven cases changes were not noted in the cells of the islands. It is possible that there may have been damaged islands in uncut portions of the pancreas.

Fibrotic Islands.—The most constant change noted was an increase in the connective tissue within the islands. This lesion has been referred to a "sclerosis" in other papers on this subject. The degree of fibrosis varied greatly in different islands of the same pancreas, and in scarcely any pancreas was there an absence of normal islands. In this the organ resembles the kidney, in which damaged and unchanged glomeruli lie side by side. We roughly classified the degree of fibrosis as (*a*) slight, (*b*) moderate or (*c*) marked, according to the extent to which the majority of islands were involved. The arrangement of the fibrous elements of a sclerosing island is like that of a tree, the trunk of which carries the blood vessel to the center of the island. Even though the fibrotic process is far advanced, the epithelial cells often

6. Otani, S.: Studies on the Islands of Langerhans in the Human Pancreas, Am. J. Path. **111**:1, 1927.

show remarkably good preservation. It is hard to believe, however, that the blood supply and the nerves are unimpaired.

Hyaline Degeneration.—All grades of hyaline change are seen, from small amounts of extracellular, pinkish-staining, homogeneous material to complete replacement of an island. In these cases, it closely resembled a hyaline glomerulus. Advanced fibrous is always present with this lesion and must be the precursor of it. A late, though not a common, process is calcification of these hyaline areas. Mallory [7] mentioned this condition in his textbook. We had one example of this in case 86, in a woman, aged 66, who had had symptoms for four years. The pancreas showed marked fat invasion, marked interstitial fibrosis of the acinar portions and extreme thickening of the arteries with calcified media. The islands varied from partial to complete hyalinization, and many were stained blue, the same color as the media of the artery.

Hemochromatosis.—Seven of the patients had diabetes which was secondary to hemochromatosis. Two of the patients appeared not to have recognizable islands. Five showed definite fibrosis, but no hyaline change. The island cells had varying amounts of pigment, but were not otherwise different from the usual appearance of a natural cell.

Pyknotic Changes.—In a limited number of cases, the islands stood out very clearly from the acinar tissue, owing to the fact that the nuclei were more deeply stained. On close examination the cells were seen to have small, darkly-stained nuclei, the chromatin network of which was nevertheless distinct. The cytoplasm was strongly acidophil. Of this group, only two showed evidence of insular fibrosis and in three giant nuclei were found. The other cases of this group did not show any change except in the pyknotic islands. That this is not a post-mortem change is clearly shown by the fact that there was no autolysis of the parenchyma as a whole in the region of the islands and that the pyknotic islands were seen in cases in which autopsy was performed early; that is, in case 104, one and a quarter hours post mortem and in cases 107 and 108, two hours post mortem. The average age of this group is the youngest of any in our series. Of the fifteen patients, one half died before the age of 40. Four died in their second decade, two in their third and two in their fourth.

Hemorrhage.—In four cases, hemorrhage into the islands occurred. This was confined to the islands and did not appear in the surrounding parenchyma. One also showed slight fibrosis and another marked fibrosis of the islands. A third presented pyknotic islands and giant nuclei. The causes of death in the patients were lobar pneumonia, diabetic coma, cardiac failure and suppurative nephritis.

7. Mallory, T. B.: Principles of Pathological Histology, Philadelphia, W. B. Saunders Company, 1918, p. 521.

Giant Nuclei.—Slight variation in the size of the nuclei is expected, and this is one of the differentiating points between the alpha and beta island cells. Occasionally one sees an island with one or two nuclei about four times the diameter of its fellows. These do not differ in any respect from the other cells except in size. One of these five cases did not show other changes in the islands. The other cases were associated with pyknotic islands, and in one of them hemorrhage was present in an island.

CLINICAL SYMPTOMS

It soon became apparent to us that there were difficulties in estimating the severity of the diabetes in any given case on the evidence at hand in the clinical records. Estimations of blood sugar were made under varying conditions; patients were admitted and died from the effects of acute infections or from postoperative shock; in short, there was no criterion by which one could say with any scientific accuracy that a patient had mild or severe diabetes. We present the comments below for what they are worth.

Coma.—There were fourteen cases of true diabetic coma uncomplicated by nephritis or infection. The following figures show the distribution according to damage of the islands: normal islands, one; pyknotic islands, one; slight fibrosis, three; moderate fibrosis, three; marked fibrosis, three, and hyaline islands, three. From this, it would appear that the degree of damage to the islands has little to do with the onset of coma. Of course, the series is small.

Gangrene.—Twenty-three patients between the ages of 45 and 62 had gangrene of the extremities. Of those who lived beyond the age of 40, more than one in five developed gangrene. Seventy-five cases of the patients with gangrene had marked generalized arteriosclerosis and thirteen per cent had only moderate arteriosclerotic changes. The following figures give the relation of gangrene to damage of the islands: normal islands, in four cases, or 36 per cent of the group; pyknotic islands, three, or 20 per cent; slight fibrosis, seven, or 23 per cent; moderate fibrosis, two, or 9 per cent; marked fibrosis, five, or 20 per cent, and hyaline islands, two, or 7 per cent. Here, again, there does not appear to be any relation between the degree of change in the islands and the incidence of gangrene. It is highest in those showing the least damage and lowest in the hyaline group.

ANALYSIS OF SYMPTOMS IN CASES SHOWING ONLY NORMAL ISLANDS

Three patients had symptoms of less than six months' duration. Five had symptoms for from two to twelve years before death. In three cases, there was no record as to the duration or the symptoms. Six of the eleven patients were sugarfree on a diet without insulin.

Three died before a special diet was instituted, that is, within a few hours after admission. These data are suggestive, but again the series is too small to draw conclusions.

SUMMARY

1. A study of 147 cases of diabetes mellitus in which autopsy was performed was made with particular reference to the pathologic structure of the pancreas and the clinical course of the disease.

2. Interstitial pancreatitis was found in 123 cases, seventy-nine of which showed well advanced lesions. While this condition is more frequently present in older persons, it is often found in middle-aged persons. An explanation for this is offered in six cases showing acute inflammation of the interstitial tissue of the pancreas. A direct relation was found between the incidence of interstitial pancreatitis and lesions of the insular tissue (table 2). Tuberculous lesions in the pancreas were not found in any case.

3. Lipomatosis of the pancreas is a late result of atrophy of the acinar tissue due to interstitial pancreatitis.

4. Definite lesions of the islands of Langerhans were found in all but eleven of the cases studied. These lesions varied from difference in the staining reactions of the cells to fibrosis of the islands and hyaline degeneration. One case of calcified islands was seen.

5. No relation was found between the type of cases in which gangrene was present and the degree of damage to the islands. The same is true of coma.

6. An analysis of eleven cases without apparent damage to the islands showed that six patients did not have glycosuria when placed on a diet without insulin.

7. It is hoped that a simple test may be devised to enable one to correlate the severity of the diabetic condition. Until this has been done, it seems impossible to relate the clinical and pathologic observations in diabetes mellitus.

THE EFFECT OF SYNTHALIN ON THE RESPIRATORY QUOTIENT OF THE DIABETIC PATIENT *

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PHILADELPHIA

In 1926, Frank, Nothmann and Wagner [1] isolated a guanidine derivative, a diguanidyl decamethylene, which they called "Synthalin." This was reported to be effective in reducing blood sugar when taken by mouth and was suggested as a substitute for insulin in the treatment of diabetes. Numerous publications have appeared, especially in Europe, concerning its use in diabetes and the possible mechanism of its action. A supply of synthalin [2] was obtained for therapeutic trial on diabetic patients. During the course of this investigation, a study was made of the respiratory quotients after a meal of dextrose. It is believed that any drug reputed to have an insulin-like action must manifest itself by an increased oxidation of carbohydrate in the diabetic organism. Blatherwick, Sahyun and Hill [3] stated that synthalin may possibly produce a hypoglycemia by an insulin-like action or by interfering with normal glyconeogenesis because of injury to the liver. The present work supports the idea that synthalin does have an insulin-like action in that it aids in the utilization of carbohydrate in the diabetic organism. Because of its toxicity, we believe that its clinical use is contraindicated. The data in this paper are presented only as evidence concerning the possible mechanism of the influence of this guanidine derivative on carbohydrate metabolism.

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1. Frank, E.; Nothmann, M., and Wagner, A.: Klin. Wchnschr. **5:** 2100, 1926.

2. Synthalin was supplied through the courtesy of Eli Lilly & Company, Indianapolis.

3. Blatherwick, N. R.; Sahyun, M., and Hill, E.: J. Biol. Chem. **75:** 671, 1927.

EXPERIMENTAL DATA

Patients were selected at random, some with mild, others with severe cases of diabetes. They were kept in bed in the morning without breakfast; a blood sugar determination was taken while fasting, a specimen of urine obtained and the expired air collected in a Tissot spirometer for a period of ten minutes. The expired air was analyzed for carbon dioxide, oxygen and nitrogen with a Henderson-Haldane gas analysis apparatus. As the collection of urine from patients over short periods was unreliable, we assumed that 15 per cent of the total calories came from protein rather than attempt to calculate the protein metabolism from the nitrogen in the urine. After the total calories from the oxygen consumption were obtained, the calories produced by the oxidation of carbohydrate were determined by the triangular map of DuBois.[4] The grams of carbohydrate utilized were calculated by dividing the carbohydrate calories by 4.1. Approximately one hour after the blood sugar during fasting was taken a meal of dextrose was given, generally 0.5 Gm. of dextrose per kilogram of body weight; in one patient with a mild case of diabetes, however, 1.5 Gm. was administered. The blood sugar was then measured at intervals of one-half, one, two and three hours. Specimens of urine were collected for three hourly periods. Collections of expired air were made at approximately three-quarter hour intervals for the three-hour period. Special attention was paid to the attainment of normal respiration in all patients, as over or under ventilation causes appreciable error in the respiratory quotient. For the periods in which the patient received synthalin, these experiments were duplicated as closely as possible, with the exception that synthalin was given one or more hours previous to the meal of dextrose. As a preparation for both the control periods and the periods during which synthalin was given, the administration of insulin was discontinued at a similar time, previous to both experiments and for a sufficient interval to obviate appreciable effects of the insulin on the utilization of carbohydrate. The determinations for blood sugar were made by the method of Folin and Wu,[5] and the presence of sugar in the urine was determined by the method of Sumner.[6] A similar study of the respiratory quotient has been used by Petty and Stoner[7] to differentiate diabetes from benign glycosurias. Repeated studies have confirmed the observation that the respiratory quotient of patients with true cases of diabetes will not rise

4. DuBois, E. F.: J. Biol. Chem. **59**: 43, 1924.
5. Folin, O., and Wu, H.: J. Biol. Chem. **41**: 367, 1920.
6. Sumner, J. B.: J. Biol. Chem. **62**: 287, 1924.
7. Petty, O. H., and Stoner, W. H.: Am. J. M. Sc. **171**: 842, 1926.

appreciably after a meal of dextrose, while patients with so-called renal diabetes give a normal response, with the respiratory quotient approaching 1.

REPORT OF CASES

CASE 1.—J. W., a man, aged 62, who weighed 77.1 Kg. and whose height was 168 cm., had a mild case of diabetes. He was admitted to the hospital on June 10, 1927, with an infected foot which was incised and drained. He was discharged from the hospital on July 28, 1927, and reported to the outpatient department regularly. The diabetes was controlled with diet. He was readmitted to the ward on Aug. 30 and Sept. 2, 1927, for the studies on the respiratory quotient.

TABLE 1.—*Results of Studies on the Respiratory Quotient in Case 1*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
Aug. 30									
8:00.....	85	0							
8:50.....	...	...	53.2	3.29	16.87	13.66	0.759	64.7	9
9:00.....	Given 38 Gm. of dextrose by mouth								
9:30.....	152								
9:45.....	...	...	57	3.31	16.96	14.26	0.784	68.1	15.6
10:00.....	176	0							
10:30.....	...	...	63.3	3.32	17.09	15.19	0.820	73.3	23.4
11:00.....	166	0							
11:15.....	...	...	57.8	3.19	17.24	13.32	0.819	64.3	22.5
11:45.....	...	...	57.9	3.22	17.20	13.52	0.817	65.2	22.1
12:00.....	140	0							
Dextrose burned in three hour period after meal of dextrose = 15.6 Gm.									
Sept. 2									
8:10.....	...	...	54.7	3.26	16.98	13.62	0.775	65.0	18
8:20.....	98	0	Given 80 mg. of synthalin by mouth						
9:00.....	...	...	Given 38 Gm. of dextrose by mouth						
9:20.....	...	...	58.8	3.32	17.06	14.28	0.811	68.7	22.7
9:30.....	118								
10:00.....	131	0							
10:15.....	...	...	68.1	3.13	17.67	13.56	0.931	67.4	49.2
10:45 ...	...	...	67.8	3.11	17.56	14.10	0.886	69.2	40.8
11:00.....	65	0							
11:15.....	...	...	66.3	3.11	17.57	13.73	0.890	67.4	40
11:45.....	...	...	60.4	3.09	17.45	13.08	0.846	63.6	28.6
Dextrose burned in three hour period after meal of dextrose = 25 Gm.									

CASE 2.—H. R., a man, aged 66, who weighed 69 Kg. and whose height was 178 cm., had a moderately severe case of diabetes; he had been treated for this condition since 1922. The patient had had many admissions to the hospital, and at the time the studies on the respiratory quotient were made he was employed as an orderly. An apparent cirrhosis of the liver and an old pulmonary tuberculous lesion were present, which later became active and from which he recently died. At the time the studies on the respiratory quotient were made, the diabetes was controlled with a prescribed diet and from 25 to 30 units of insulin daily.

CASE 3.—J. I., a man, aged 23, who weighed 59 Kg. and whose height was 184 cm., had a moderately severe case of diabetes. He required a prescribed diet and from 25 to 30 units of insulin daily. He had noted the symptoms of diabetes only three months previous to the present examination. He was admitted to the hospital on Sept. 1, 1927, and discharged to the outpatient department on Oct. 10, 1927. He received from 25 to 30 units of insulin daily with a prescribed diet until synthalin therapy was substituted, which was maintained until the diabetes was controlled by diet alone. He has since taken some insulin.

TABLE 2.—*Results of Studies on the Respiratory Quotient in Case 2*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
Aug. 26									
8:00	115	0							
8:30	...	...	43.9	4	15.88	14.04	0.740	66.4	4.6
9:00	Given 35 Gm. of dextrose by mouth								
9:30	203	0							
9:45	...	...	53.1	3.75	16.45	14.94	0.791	71.6	17.9
10:00	243	0							
10:30	...	...	54.6	3.51	16.84	13.92	0.814	67.1	22.1
11:00	185	0							
11:15	...	...	53	3.49	16.72	14.06	0.781	67.2	14.8
11:45	...	...	54.3	3.48	16.82	13.98	0.800	67.1	18.8
Dextrose burned in three hour period after meal of dextrose = 14 Gm.									
Aug. 29									
8:00	137	0	37.3	4.29	15.54	12.78	0.746	60.5	5.4
8:10	Given 60 mg. of synthalin by mouth								
9:00	100	0	42	4.25	15.65	14.04	0.756	66.7	8
9:15	Given 35 Gm. of dextrose by mouth								
9:45	139								
10:00	...	...	49.9	3.86	16.33	14.46	0.793	69.4	18
10:15	183	0							
10:45	...	...	42.8	4	16.04	13.20	0.768	62.8	11.3
11:15	200	0							
11:30	...	...	49.4	3.95	16.44	13.86	0.841	67.2	29.6
12:00	...	...	51.6	3.71	16.58	14.04	0.808	67.5	21.6
12:15	134	0							
Dextrose burned in three hour period after meal of dextrose = 13.5 Gm.									
Sept. 20									
8:00	124	0	Given 50 mg. of synthalin by mouth						
9:10	...	...	58	3.01	17.17	13.82	0.748	65.5	6.6
9:20	142	...	Given 35 Gm. of dextrose by mouth						
9:50	150								
10:05	...	...	60.9	3.19	17.23	14.03	0.820	67.7	24.4
10:20	157	0							
10:50	...	...	58.2	3.13	17.15	13.83	0.780	66.1	14.5
11:20	134	0							
11:35	...	...	62.2	3.17	17.21	14.48	0.806	69.7	21.6
12:05	...	...	64.4	3.13	17.47	13.79	0.865	67.3	35.7
12:20	122								
Dextrose burned in three hour period after meal of dextrose = 16.7 Gm.									

TABLE 3.—*Results of Studies on the Respiratory Quotient in Case 3*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
Sept. 9									
8:00	150	+							
8:45	...	...	61.6	2.69	17.83	11.93	0.820	57.6	20.4
9:00	...	1.9	Given 30 Gm. of dextrose by mouth						
9:30	168								
9:45	...	...	57.3	2.74	17.76	11.35	0.818	54.8	19.2
10:00	183	2.7							
10:30	...	...	50.8	2.79	17.30	11.79	0.711	55.3	0
11:00	203	6.5							
11:30	...	...	65.2	2.61	17.88	12.49	0.806	60.1	18
12:00	207	4.5							
Dextrose burned in three hour period after meal of dextrose = 9.1 Gm.									
Sept. 12									
6:00	...	...	Given 30 mg. of synthalin by mouth						
8:00	150	0	Given 60 mg. of synthalin by mouth						
8:40	...	...	71.6	2.58	18.21	11.94	0.914	59	40
9:00	...	0	Given 30 Gm. of dextrose by mouth						
9:30	176								
9:45	...	...	69	2.63	17.98	12.68	0.845	61.0	27.2
10:00	197	1.7							
10:15	...	...	60.3	2.71	17.82	11.72	0.824	56.6	21.5
10:45	...	...	71.1	2.71	18.04	12.63	0.902	62.2	39.8
11:00	200	2.2							
11:15	...	...	80.1	2.43	18.33	12.84	0.895	63.2	39
11:45	...	...	78.6	2.48	18.30	12.67	0.907	62.6	41.3
12:00	166	0							
Dextrose burned in three hour period after meal of dextrose = 23.9 Gm.									
Sept. 13									
8:00	111	0							
8:45	...	...	61.6	2.57	17.91	11.68	0.801	56.1	16.5
9:00	...	0	Given 30 Gm. of dextrose by mouth						
9:45	...	...	67.2	2.35	18.09	12.00	0.772	57.4	10.9
10:00	157	0							
10:30	...	...	61.2	2.55	18.00	11.20	0.822	54.3	20.4
11:00	183	0							
11:30	...	...	67.7	2.44	18.22	11.37	0.857	55.4	26.6
12:00	115	0							
Dextrose burned in three hour period after meal of dextrose = 14.1 Gm.									

CASE 4.—H. S., a man, aged 57, who weighed 54 Kg. and whose height was 160 cm., had a mild case of diabetes. He was admitted to the hospital on July 18, 1927, and discharged on Aug. 20, 1927. The diabetes was usually controlled by diet alone.

CASE 5.—H. L., a youth, aged 16, who weighed 67.4 Kg. and whose height was 190 cm., had a severe case of diabetes. He required a prescribed diet and from 70 to 80 units of insulin daily, although he was occasionally suspected of cheating on his diet. He also had hyperthyroidism and indications of other endocrine dysfunction. At the time of the experiments, his basal metabolic rate was plus 30 to 35. He had had numerous admissions to the hospital.

TABLE 4.—*Results of the Studies on the Respiratory Quotient in Case 4*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
July 26									
8:00	91	0							
8:45	...	...	43.5	3.27	16.89	11.11	0.758	52.8	6.9
9:10	...	...	Given 125 Gm. of dextrose by mouth						
9:20	134	0							
9:40	217								
9:55	...	...	49.1	3.28	16.90	12.53	0.762	59.5	8.9
10:10	393	1							
10:25	...	...	55.1	3.24	17.17	12.95	0.816	62.5	21.3
10:55	...	...	60.5	3.26	17.10	14.51	0.805	69.8	20.9
11:10	251	7.3							
11:25	...	...	52.1	3.25	17.24	11.98	0.838	58.1	24.4
11:55	...	...	54.2	3.18	17.39	11.90	0.857	58	27.8
12:10	150	1.9							
Dextrose burned in three hour period after meal of dextrose = 13.7 Gm.									
Aug. 19									
8:00	102	0	Given 40 mg. of synthalin by mouth						
8:45	...	...	42.4	3.65	16.67	11.29	0.813	54.3	18.7
9:00	...	0	Given 125 Gm. of dextrose by mouth						
9:30	129								
9:45	...	...	52.7	3.10	17.58	10.88	0.889	53.4	32
10:00	183	0							
10:15	...	...	55.5	3.27	17.52	11.55	0.931	57.3	41.8
10:45	...	...	55.8	3.16	17.08	11.02	0.948	54.9	43.9
11:00	109	0							
11:15	...	...	53.6	3.23	17.47	11.39	0.901	56.1	35.2
11:45	...	...	53.7	3.25	17.54	11.12	0.930	55.1	40.2
12:00	100	0							
Dextrose burned in three hour period after meal of dextrose = 27.5 Gm.									

CASE 6.—E. B., a man, aged 38, who weighed 67 Kg. and whose height was 175 cm., had a moderately severe case of diabetes. He had noted the symptoms for about six months. He required a prescribed diet and approximately 35 units of insulin daily to control the diabetes. There were some indications of a slight hyperthyroidism.

COMMENT

The dextrose tolerance, as measured by the sugar in the blood and urine after a meal of dextrose, was notably improved during the period in which synthalin was given to the two patients with mild cases of diabetes, cases 1 and 4. In case 3, although the blood sugar curve was similar to that of the control subject, there was a marked decrease in urinary sugar. When the test was repeated a day later, without the use of any drug in the interim, the height of the blood sugar curve was much

decreased, although the respiratory quotients were similar to those during the control period. The patient in case 5 did not show any improvement in tolerance. The patient in case 2 showed a slight improvement with the use of synthalin, and a marked improvement three weeks later,

TABLE 5.—*Results of Studies on the Respiratory Quotient in Case 5*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour	Calories from Oxidation of Carbohydrate per Hour
Sept. 14									
8:00	157	0							
8:45	...	...	94.4	3.38	16.59	23.11	0.724	122.8	1.2
9:00	...	0	Given 33 Gm. of dextrose by mouth						
9:30	234								
9:45	...	...	88.8	3.39	16.61	24.46	0.729	115.3	3.4
10:00	243	5.7							
10:30	...	...	82.4	3.56	16.32	24.28	0.716	114.2	0
11:00	251	9.8							
11:15	...	...	83.7	3.34	16.50	23.80	0.696	116.4	0
11:45	...	...	89.7	3.32	16.63	24.65	0.716	115.9	0
12:00	203	5.6							
	Dextrose burned in three hour period after meal of dextrose = 0.8 Gm.								
Sept. 16*									
8:00	183	0							
8:50	...	...	65.3†	4.40	15.48	22.53	0.758	107	14
9:00	193	0	Given 33 Gm. of dextrose by mouth						
9:30	243								
9:45	...	...	85.9	3.79	16.41	24.38	0.792	117.1	30.4
10:00	268	6.5							
10:30	...	...	84.7	3.35	16.75	22.46	0.748	106.5	9.5
11:00	224	6.2							
11:15	...	...	78.1	3.74	16.28	23.01	0.753	109.1	13
11:45	...	...	87.3	3.65	16.25	26.03	0.726	122.6	3.6
12:00	203	5.7							
	Dextrose burned in three hour period after meal of dextrose = 11.8 Gm.								

* Previous to the experiment made on September 16, the patient was given synthalin as follows: September 15, 12 noon, 20 mg.; 4:30 p. m., 30 mg.; 12 midnight, 20 mg.; September 16, 8 a. m., 30 mg.

† The low ten minute volume was due to the leaking of the valve on the spirometer side causing some rebreathing.

TABLE 6.—*Results of Studies on the Respiratory Quotient in Case 6*

Time	Blood Sugar, Mg.	Urine; Dextrose, per Hour, Gm.	Expired Air: 10 Minute Volume, Liters	Expired Air: Carbon Dioxide, per Cent	Expired Air: Oxygen, per Cent	Oxygen Intake per Hour, Liters	Respiratory Quotient	Total Calories per Hour
8:00	224	2						
9:05	...	...	57.8	3.71	16.41	16.51	0.771	78.6
9:15	Given 60 mg. of synthalin by mouth							
10:00	...	...	58	3.63	16.41	16.54	0.756	78.6
10:15	197	2.5						
11:00	...	...	62.3	3.41	16.72	16.61	0.769	78.9
11:15	166	2.6						
11:35	...	...	65.5	3.24	16.85	16.99	0.741	80.3
12:10	...	...	63.9	3.34	16.83	16.52	0.766	78.7
12:15	180	1.5						

although these data are vitiated by the long interval between the tests during which time the patient received synthalin daily.

In four of the five cases, there was an increase in the respiratory quotients during the periods in which synthalin was given, over those during the control periods, indicating that more carbohydrate was being

utilized after the patient had been given synthalin. This increase amounts to from 10 to 15 Gm. of carbohydrate in the three-hour period studied. The patient in case 2 did not show this increase in utilization, although the diabetes was controlled for a number of weeks by diet with the aid of synthalin. It is important to consider the rate of ventilation in these experiments, as overventilation may easily increase the amount of carbon dioxide loss from the body and give a misleading high respiratory quotient. A comparison between the period in which synthalin was given and the control period of the average volume of expired air in the ten minute periods after the meals of dextrose had been given gives data which indicate that the higher respiratory quotients during the periods in which synthalin was given were not due to overventilation. This is possibly not true in the patient in case 3, whose rate of ventilation was appreciably higher during the period in which synthalin was given, and which was rather irregular throughout the experiments. In case 4, the results might seem to lose their significance because of the long interval between the control experiment and the experiment with synthalin. However, this case was used in a similar experiment on the respiratory quotient with another drug shortly before the study with synthalin. The results are not recorded in table 3, but they showed data on the sugar tolerance and the respiratory quotient similar to the control experiment.

Similar studies to those reported here have been made by A. Lublin.[8] He found in two rather severe cases of diabetes that after the patient had taken a meal of dextrose the respiratory quotient rose higher after previous synthalin therapy than in the control period when no drug had been given. In contrast to the present experiments, Lublin gave synthalin the day previous to the test, in one case 40 mg., and in the other 75 mg. In one patient (case 3) on whom we performed the test both immediately after he had received the synthalin and twenty-four hours later, we found a response of the respiratory quotient only in the former test while the latter was similar to that of the control period. In view of the reputed slower action of synthalin, it is surprising to note the quick response which was obtained in the present experiments.

Recent studies on the relation of synthalin to carbohydrate metabolism have been made by R. Bodo and H. P. Marks.[9] They were able to produce a marked hypoglycemia in rabbits, provided a sufficiently large dose was given parenterally. Rabbits killed during the time the hypoglycemia was present showed a decrease in the glycogen of the liver, which result is in contrast to the action of insulin. In the eviscerated cat from which the spinal column had been removed, and in the perfused

8. Lublin, A.: Arch. f. exper. Path. u. Pharmacol. **124:** 118, 1927.

9. Bodo, R., and Marks, H. P.: J. Physiol. **65:** 83, 1928.

hind leg of a dog, the application of synthalin caused a disappearance of blood sugar. There was a decrease in the glycogen of the muscle, and respiratory experiments showed a decrease in oxygen consumption of the preparation. As the sugar which disappeared from the blood was neither burned nor stored, the authors sought another explanation for the phenomenon. The lactic acid of the blood was appreciably increased, and the respiratory quotients of the preparations rose above unity. These data suggest that the explanation of the mechanism of synthalin which reduces the blood sugar may be principally in the formation of lactic acid.

These experiments are of interest in relation to the present studies on the respiratory quotients. It might be possible that the apparent rise in the respiratory quotient after the administration of synthalin could be due to the formation of lactic acid which liberates carbon dioxide from the blood. If this was the case, it was thought possible that synthalin administered to a patient without dextrose would cause an apparent rise in the respiratory quotient. Case 6 was studied with this in mind. On the day previous to the experiment the patient was given 20 units of insulin at 7:30 a. m. and 5 units at noon; then the administration of insulin was discontinued, and synthalin was given as indicated in chart 6. Under these conditions the synthalin did not cause an increase in the respiratory quotient or a decrease in the consumption of oxygen. There was also no decrease in the consumption of oxygen in the other cases studied when the period in which synthalin was given was compared with the control period. The lactic acid of the blood in case 6 was determined before and after the administration of synthalin, and an appreciable increase was not noted. While the evidence is not at all complete, it would seem possible that the formation of lactic acid alone is not sufficient to explain the increase of the respiratory quotients in the present experiments.

Many investigators have considered the toxic action of synthalin on the liver, and mention has been made of its nephrotoxicity. We have certain data (being prepared for publication) which substantiate these views and emphasize the nephrotoxic action. We do not have any intention, in this paper, of advocating the use of synthalin as a substitute for insulin in the treatment of diabetes, but merely suggest that synthalin does have an insulin-like action on the respiratory quotient of the diabetic patient.

CONCLUSIONS

Synthalin, when given before a meal of dextrose, tends to increase the utilization of carbohydrate in the diabetic patient. This is indicated by an increase in the respiratory quotient during the three hours after a meal of dextrose when compared with a similar period before which synthalin was not given. The increase in utilization amounts to 10 or

15 Gm. of carbohydrate during this period. One patient failed to show such a response.

Some of the patients responded to synthalin therapy by an increase in the tolerance for dextrose as measured by the sugar in the blood and urine.

Because of accumulating evidence of the toxicity of synthalin for the human organism, the data in this paper are presented as suggestions for the mechanism of its action and are not to be interpreted as an advocation of its clinical use.

THE REDUCING POWER (BLOOD SUGAR) OF FILTRATES FROM THE BLOOD OF THE RABBIT *

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Since the advent of insulin, the rabbit has been used so much for experiments which involve the determination of blood sugar that it seemed worth while to collect some of the material which has accumulated in our laboratory and treat it in such a manner as to reveal something of the behavior of the blood sugar in the normal animal.

The necessity of multiple observations seems to be generally accepted if one is to judge from the work appearing currently. As soon as multiple observations are made numerous problems arise, such as the number of observations which must be made before conclusions are warranted; the best manner of assembling observations so as to present the behavior of the series as a whole and at the same time give the reader a concrete mental picture of the behavior of the group; the constitution of the group of subjects; the effects of the nutritional condition of the subjects; whether or not the time of year or the time of day at which the observations were made affects the results, and so on. It is the purpose of this paper to present the results of a study of the importance of some of these factors in work on the blood sugar of the rabbit.

A NORM FOR THE BLOOD SUGAR OF THE RABBIT

As the first step in the experimental part of the present study, it is sought to establish a norm for the blood sugar of the rabbit with a fair degree of precision. Shaffer and Hartmann's [1] method for the determination of sugar was used, with the conversion table of Duggan and Scott.[2] The blood was obtained from a vein of the ear. Petrolatum was always applied to the ear, and the blood was allowed to drop into a small dish containing a small amount of dry sodium oxalate in order to prevent coagulation. From this dish, the blood was drawn into a calibrated pipet from which it was measured into 7 cc. of water, and the protein precipitant was then added to the mixture. It was usually

* Submitted for publication, Oct. 22, 1928.

* From the Department of Physiology, Columbia University.

1. Shaffer, P. A., and Hartmann, A. F.: J. Biol. Chem. **45**:365, 1920-1921.
2. Duggan, W. F., and Scott, E. L.: J. Biol. Chem. **67**:287 (Jan.) 1926.

necessary to use xylene to induce hyperemia and a freer flow of blood. The customary precautions to avoid excitation of the animal were observed.

Variation in the technic of analysis was insignificant in comparison with the physiologic variations encountered (table 1).

The usual value for ϵ (Scott [3]) was of the order of 12 mg. per hundred cubic centimeters of blood. Following the customary procedure of carrying ϵ to two significant places when the first digit is less than 8 and reporting the individual results to the same decimal place, we would be warranted in reporting the results in milligrams. Since the indicated precision of the method is milligrams, this is the practice which has been followed in the tables. In view of the rather large mean deviation among the observations and of the deviation in the deter-

TABLE 1.—*Results of Multiple Determinations of Blood Sugar*

Date	Animal	Condition	Blood Sugar Observed						ϵ
11/19/21	Beef	Abattoir	87	89	89	94	99	92	±4.9
	Rabbit	Normal	144 141	141 139	144 144	147 141	144 147	143	±2.5
11/22/27	Rabbit 271	Normal	121	121	123	123	121	122	±1.1
	Rabbit 262	Normal	126	123	123	121	126	124	±2.2
	Rabbit 307	Normal	129	116	116	123	...	121	±6.2
11/23/27	Cat	Ether	283 283	281 281	279 281	281 286	279 289	281	±2.5
11/28/27	Cat	Ether	251	246	249	251	...	249	±1.9
11/29/27	Rabbit 307	Normal	110	110	113	110	113	111	±1.1
Mean ϵ									2.8

minations per se as indicated in table 1, it is difficult to see just what the significance of the final place would be. Accordingly, in making calculations it has been our usual practice to round off the values to even multiples of 5. This greatly facilitates the process of calculation and can introduce no interpretative error. In cases in which the result was just midway between two multiples of 5, the nearest even multiple was chosen. Thus, 122.5 and 117.5 would each be treated as 120.

All of the determinations reported in this series were made by a single analyst. In some instances, the observations reported were isolated, while in others they were the initial observations in the studies on the blood sugar curve. In the latter case, the specimen of blood which was used in the study was taken just before the administration of insulin or of sugar. When only one specimen was drawn, the observations were not repeated at intervals of less than one day, except in an insignificant number of cases. When the animals were subjected to further experimentation, they were allowed at least one week for recovery.

3. Scott, E. L.: J. Biol. Chem. **73**:81 (May) 1927.

The animals were obtained from a dealer in the open market and were not especially bred for uniformity. Had this been done there is little doubt that greater precision would have resulted (Riddle and Honeywell [4]).

We had found by previous experience that rabbits could be kept in good condition for long periods on a mixed diet of oats, hay and cabbage. This diet was used throughout the time in which these data were collected. The specimen of blood was drawn just after the animals were removed from the pens where they had free access to both food and water. This method was followed because it was thought that the condition more nearly represented the normal (in the sense of usual) condition of the animal than would that which existed after a period of inanition. Later in this paper the possible advantage in precision which may be gained by subjecting the animals to a short period of inanition before the specimen of blood is taken will be discussed. The data were collected over a somewhat prolonged period—from December, 1924, to August, 1927—as well as from a somewhat heterogeneous group of rabbits. No doubt these facts tend to increase the variations in the results but, at the same time, they make the results more representative of the general field. If variation in different animals and from time to time in the same animal is an intrinsic property of the blood sugar level in rabbits, this property cannot be made evident nor its causes worked out by establishing such artificial conditions as to eliminate it. It is true that there may be times when it is necessary to obtain the greatest possible precision, as in the assay of insulin, but care must be exercised as to the relation of this precision to the value of generalizations based on such experiments.

The series consists of 1,625 observations made on 215 rabbits. The results are published seriatum in table 2, and some of the general properties of the series are shown in chart 1. There was no selection or omission other than that necessary to make the series conform to the description in the preceding paragraphs.

As the rabbits were purchased in the open market, we did not have a record of their ages, but apparently they were in early sexual maturity when they were received. With few exceptions they were not used in this research longer than three months, although eleven were in use for periods varying from five to nine months, one for one year and nine months and one for two years and three months. In none of those used for the longer periods was there any consistent or progressive change which could be attributed to advancing age.

As the rabbits increased in weight during their stay in the laboratory, any possible relationship between body weight and blood sugar level

4. Riddle, O., and Honeywell, H. E.: Am. J. Physiol. **67**:317 and 337, 1923-1924.

TABLE 2.—*Results of 1,625 Observations on 215 Rabbits*

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
123	128	122	96	130	96	125	122	112	112	116	94	105	160	112	136	121	136	123	118	121	131	102	97	134	124	113	123	131	126	139	121	131
138	130	118	116	128	116	132	125	108	122	114	112	119	125	128	121	118	102	136	113	121	134	99	110	141	123	118	107	125	129	131	139	126
128	114	114	150	105	128	116	128	114	125	105	130	135	125	132	118	126	105	131	121	113	106	105	115	124	110	121	118	110	139	113	121	121
130	119	114	144	93	140	128	102	132	130	94	135	105	116	114	149	116	131	118	141	107	113	105	118	134	123	123	123	113	121	139	121	139
116	128	128	122	128	145	148	108	130	116	114	148	149	128	125	147	129	123	113	118	107	105	118	122	132	123	123	107	120	121	123	118	136
102	125	128	119	128	102	132	108	108	166	105	80	145	128	148	144	126	134	110	126	118	107	94	126	121	136	121	139	124	118	118	118	126
112	128	124	112	130	122	128	125	112	128	130	102	125	112	112	121	116	116	113	152	118	105	107	121	118	116	113	118	121	129	121	139	121
114	135	124	116	122	92	142	119	112	128	157	94	125	122	119	110	123	123	118	118	126	89	121	130	106	123	107	129	130	131	121	136	131
112	125	116	112	119	128	151	94	122	154	142	130	145	138	122	131	121	121	118	111	136	134	110	118	130	141	131	144	145	113	129	129	131
102	125	122	110	112	142	116	116	128	160	135	110	135	122	110	134	118	105	134	107	110	99	110	106	113	110	110	139	129	107	123	126	136
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116	154	112	122	102	116	112	132	116	160	140	122	130	130	142	123	105	118	118	105	113	110	116	129	126	136	136	132	121	135	125	121	121
112	122	114	141	112	138	119	132	110	122	125	138	135	116	128	107	118	116	123	109	105	134	136	116	113	134	117	125	129	139	118	118	129
116	119	118	128	102	119	116	105	122	108	119	170	145	132	130	123	134	121	129	99	131	139	116	118	97	140	127	136	134	129	121	121	121
116	154	135	125	112	105	119	114	125	132	119	128	128	122	122	113	105	123	144	109	121	139	105	118	122	136	101	126	121	139	118	134	116
102	108	130	112	130	128	112	102	105	148	130	125	122	125	128	141	136	97	185	105	107	136	121	117	121	134	129	121	126	129	113	118	131
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142	138	110	112	105	116	128	122	140	142	112	122	145	132	126	136	105	123	110	136	121	123	136	121	127	122	116	134	123	155	126	129	131
138	132	122	125	112	92	130	140	116	132	122	128	128	135	131	107	116	134	118	99	113	110	141	119	102	131	113	129	123	139	118	121	136
112	122	124	112	114	108	116	116	112	160	130	130	130	135	129	113	118	121	113	129	99	105	131	130	124	131	118	126	118	126	129	126	131
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114	142	128	122	128	128	122	154	128	132	96	102	140	125	134	123	110	105	121	105	105	107	94	130	129	121	129	118	131	118	123	131	
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119	138	105	128	112	138	116	130	128	122	130	138	135	122	136	108	121	110	121	134	99	118	89	129	118	129	110	129	113	139	118	129	
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119	130	125	122	84	96	122	151	160	110	130	99	128	128	129	125	118	121	131	97	102	126	118	106	126	114	106	126	122	123	123	129	
114	142	108	114	128	138	140	160	119	105	122	105	140	128	126	120	113	129	113	99	99	116	99	106	113	129	123	126	113	134	121	126	
110	114	116	110	124	128	102	170	158	105	119	112	125	122	123	105	113	134	131	131	131	105	94	129	110	130	123	132	126	126	129	129	
124	122	142	108	114	122	112	157	138	116	110	88	130	142	129	111	121	129	139	144	118	105	99	130	123	127	126	123	116	131	131	136	
128	130	122	110	117	134	116	116	154	145	138	114	142	125	139	134	129	113	110	136	99	113	97	116	119	140	105	139	134	134	134	123	
134	112	130	112	110	119	80	112	119	151	128	99	128	122	102	128	118	110	118	131	94	105	94	118	113	149	141	113	131	134	118	121	
112	119	119	114	132	142	74	151	148	140	92	119	142	128	107	105	131	102	134	107	110	113	94	131	105	140	118	127	121	123	131	123	
128	112	122	112	122	154	128	112	114	125	108	125	135	119	107	128	126	118	113	131	116	126	104	118	117	142	110	133	113	126	121	123	
148	144	125	119	116	130	135	128	142	135	110	128	145	125	129	123	121	134	123	105	97	105	105	126	131	121	110	131	131	139	118	121	
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130	130	112	112	102	112	138	116	160	148	96	128	119	108	157	126	129	134	136	99	99	118	99	130	129	107	122	110	129	134	136	129	
112	128	116	130	116	122	122	125	145	114	114	114	122	138	152	121	123	118	126	105	94	118	105	123	117	109	116	141	123	131	131	121	

ABSOLUTE FREQUENCY

might be thought to have a bearing on the effect of age. Should such a relationship exist it would be of interest of itself. Consequently, the correlation coefficient (r) between body weight and blood sugar for a series of 1,299 observations was calculated and found to be less than 0.08—certainly not a significant value.

Those animals which were in use for the longer periods were allowed considerable time for rest and remained in good condition. The one which was under observation for the longest time died from an undetermined cause during the summer, about two months after last having been used.

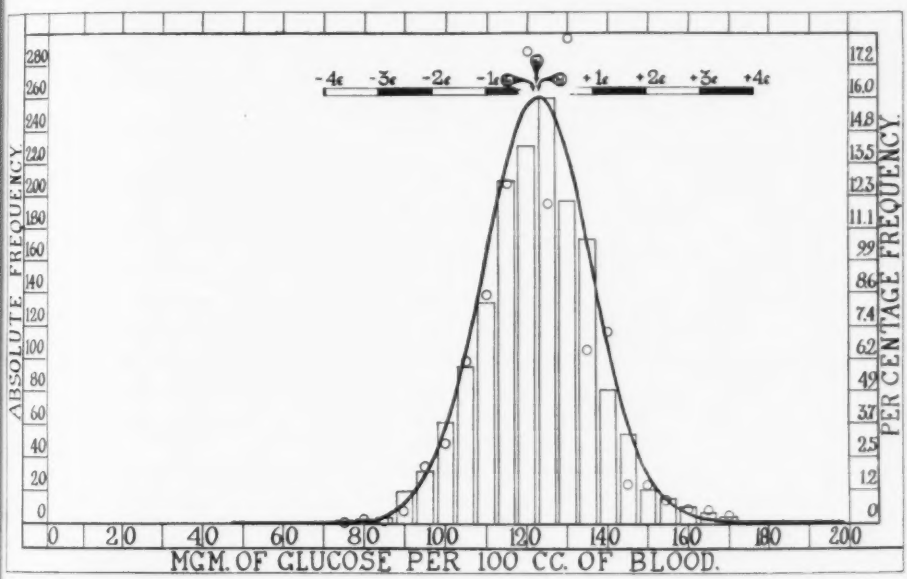

Chart 1.—General properties of the 1,625 observations made on 215 rabbits.

From the work of Riddle and Honeywell[4] on pigeons, it might possibly be expected that sex or the phenomenon of reproduction would also effect the blood sugar level in rabbits. So far our experience does not indicate that such is the case. Consequently, these factors have not been considered in the present paper. The problem, however, is of sufficient importance to warrant a special study, and it is hoped that our evidence may be presented in a later paper.

The possible effects of the season of the year or the time of day on the blood sugar level will be discussed subsequently. On the basis of the evidence presented these factors have likewise been disregarded.

As already stated, the series includes all of the observations that conformed to the conditions that have been outlined, which were obtained during the period of study. It results from this that observations were made on certain animals a great many times, while on the other hand there were 101 animals which were not used more than twice. In a later section argument is presented to show that there is probably a characteristic individual blood sugar level. From this, the possibility arises that the series has been biased by the inclusion of a large number of observations on certain animals with either a peculiarly high or low individual level.

In order to study this possibility, several subseries were selected from the grand series. These are presented (series 2 to 12 inclusive) in summarized form in table 3. The first of these series (series 2) consists of the initial observation on each animal. In this series there were 215 observations made on 215 different animals. Series 3, 4 and 5 consist of the first, second and third observation, respectively, on each of the 114 animals on which three or more observations were made. Series 6 is formed by combining series 3, 4 and 5. In doing this, a series is obtained which consists of 342 observations on 114 animals, three observations on each. In such a series there could not be any distortion due to individual peculiarities. All of the series, within the limits of expectation (Scott [3]), appear to be essentially similar in all of their properties to the grand series (table 3). It will be noted, however, that all of the observations were made early in the laboratory experience of the several animals, and that the means are all slightly below that of the grand series. The difference is less than $3\epsilon_M$ and hence of itself cannot be considered as significant, but its persistence through all of these early observations might lead one to search for possible correlated factors. There are three apparent possibilities: 1. There may be a progressive rise of the blood sugar level associated with the advancing age of the animals. In view of what has been said this does not seem to be probable. 2. It may be that it so happened that the animals on which many observations were made had an unusually high characteristic blood sugar level. 3. It may be that continued use in the laboratory is associated with an increased blood sugar level.

In the series of 1,625 rabbits, twenty-five or more observations were made on each of thirteen animals. On each of eleven animals, twenty-five observations were made within a period of six weeks. The determinations were made on isolated specimens of blood drawn at approximately daily intervals, though determinations were usually not made on Saturday or Sunday and occasionally not on other days. The animals were not used for any other purpose during the course of these observations. The 275 observations on the eleven animals were

divided into five series of fifty-five observations each. The first five observations on each animal constituted the first series; the second five, the second series, and so on through the group. The results are summarized in table 3. It will be seen that the characteristics for the 275 observations are essentially similar to those for the grand series. The mean for the first series of fifty-five rabbits (series 7, table 3), however, is unusually low, being only 118, while there is a progressive rise as the observations are accumulated (series 7 to 11, table 3).

As all of the animals were in early sexual maturity at the beginning of the period of observation, and as this was only of six weeks' duration, it hardly seems probable that advancing age could have been a significant factor in bringing about this change in the blood sugar level.

TABLE 3.—*Characteristics of Several Series of Blood Sugar Observations*

		Blood Sugar				
		M	E	FM	Md*	Mo†
2	Series of 215 initial observations	121	13.9	0.97	121	120
3	Series of 114 initial observations	121	12.8	1.20	121	121
4	Series of 114 second observations	121	14.4	1.35	121	121
5	Series of 114 third observations	121	14.6	1.37	121	121
6	Series of 342 first, second and third observations on 114 subjects	120	14.1	0.76	120	120
7	Series of 55 observations, being the first 5 observations on each of 11 subjects	118	10.4	1.40	117	115
8	Series of 55 observations, being the second 5 observations on each of 11 subjects	123	10.5	1.41	123	123
9	Series of 55 observations, being the third 5 observations on each of 11 subjects	125	10.2	1.36	125	125
10	Series of 55 observations, being the fourth 5 observations on each of 11 subjects	128	10.7	1.44	128	128
11	Series of 55 observations, being the fifth 5 observations on each of 11 subjects	128	10.5	1.41	127	125
12	Series of 275 observations, being the first 25 observations on each of 11 subjects	124	11.1	0.67	124	124
13	Series of 459 observations; curve 2 in chart 2	124	9.2	0.42	124	124
14	Series of 450 observations; curve 3 in chart 2	123	14.9	0.70	123	123
15	Series of 50 observations; curve 2 in chart 3	131	15.0	2.1	132	136
16	Series of 50 observations; curve 3 in chart 3	110	14.0	2.0	107	101

* Md indicates the median.
† Mo indicates the mode.

Again, the animals in this particular group had a low rather than a high initial mean—118 as against 121 for all initial means, or 120 for the first three observations for all animals on which three or more observations were made (table 3). It would appear from this that any bias due to individual characteristic levels would have been toward the lower rather than the upper limit. Apparently, the rise must be associated with the continued use in the laboratory. Just what is the determining factor is difficult to ascertain. So far our work does not offer an apparent clue. In the phenomenon, however, a variable is revealed which occasionally may have been overlooked in research work and which apparently may constitute a source of confusion in interpreting the results of a research. Controls should be so planned as to take account of this factor.

From all that has preceded, it seems fair to assume that the 1,625 observations, as shown in table 2 and chart 1, represent fairly the behavior of the blood sugar in rabbits that are fed, as it

exists during ordinary laboratory procedures, in which the animals are used repeatedly so long as they appear to be in good condition. When the observations are made early in the laboratory experience of the animals, a somewhat lower mean may be expected and a some-

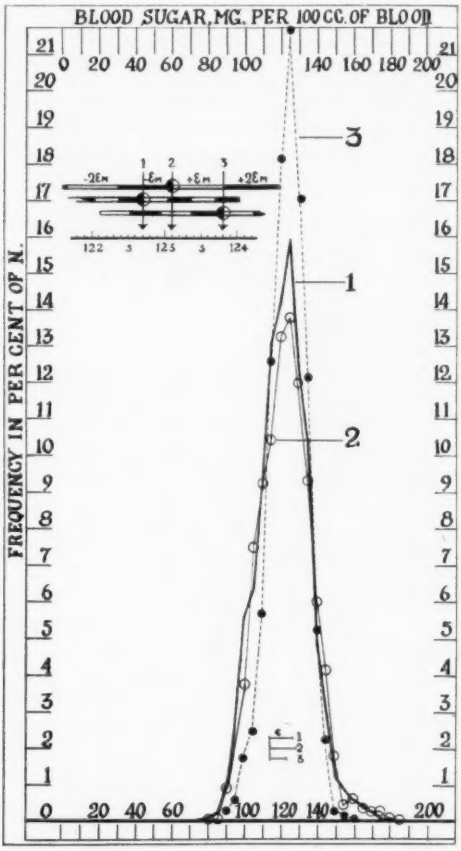

Chart 2.—Curves for the three series of observations on the blood sugar of rabbits, showing the significance and importance of the characteristics of the series, as well as the method of comparison of the series by the superposition of the frequency curves. The insert shows that the 1,625 observations of the first series are not sufficient to separate this series from the others (Scott). It should be noted that the third series is almost as good because of the greater similarity of the material.

what higher one after the rabbits have been subjected to many determinations. The precision of the results will be somewhat enhanced if the

animals selected for observation in a particular research have been subjected to approximately similar amounts of experimental use.

From work which is at present in progress in our laboratory, it appears that other properties of the series than the mean, as ϵ or the

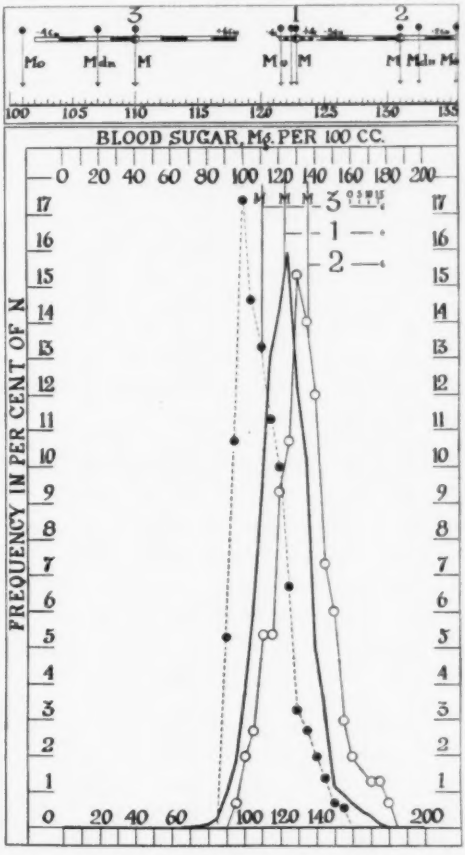

Chart 3.—Curves for groups taken from the series of 1,625 observations to illustrate the fact that dissimilar means may occur in supposedly similar subjects.

degree of skewness, may contribute information which aids distinctly in bringing out the significance of series which are being studied. For this reason it does not seem to be out of place to call attention to the behavior of some of these properties in a few series in which a considerable number of observations were made. The properties are better

shown by graphs than by the calculated values and hence charts 1 to 3 are introduced (also table 3).

In the series of 1,625 rabbits, 459 observations were made on an unusually uniform group of twenty-one rabbits within a period of about ten weeks. The results of 450 observations which were made on a rather heterogeneous group of 100 rabbits are also included. In the latter case, the period of observation extended over about three years. These two groups are natural in the sense that each resulted in the course of a specific research and they are mutually exclusive. No rabbit that was used in one appears in the other. As judged by the means alone, the results in the long series and in the two included series would have the same significance. The three series are shown in the form of frequency polygons in chart 2.

From this figure it will be seen that the data of the series of 459 rabbits do not cover the general field, and apparently it would be possible for a series with a limited range to misrepresent the center of the general field as well as the form of distribution, as is illustrated by the present case. We are not in possession of a series of this length in which such a misrepresentation has occurred; in chart 3, however, are shown frequency polygons for two series, each of fifty observations, which illustrate this possibility. The mean of each of these series differs from that of the series of 1,625 observations and from that of the other series by a significant amount as judged by the criteria of Scott,[3] which are considerably more severe than those in general use. All of the observations in these series are included in the series of 1,625 observations, and each is an integral series in which the original data were collected for a specific purpose other than that for which they are here used. As generalizations cannot legitimately be extended to populations other than that from which the data were drawn, it should be evident that too high a price may be paid for great precision. This is especially so if the precision is obtained by so close a selection of the subjects that they do not represent the field to which it is desired to extend the generalizations. The result may be true and, granted access to similar highly selected material, it may have a high degree of repeatability, but it may have such a limited significance that it is of little general value.

SEASONAL VARIATIONS

The question of seasonal variations is continually recurring (Riddle and Honeywell[4]), and if such variations exist in fact, it is a question of considerable importance for, aside from its intrinsic interest, it would be possible to compare only such series as were obtained at a corresponding time of the year or those in which the observations were distributed evenly throughout the year. The determinations on the series of 1,625 rabbits just considered, were made at the convenience of the

observers and without regard to the reason. The result is that the observations were distributed somewhat roughly, but still distributed, through the entire year. To these 1,625 observations were added 222 comparable observations which were obtained by other workers in the laboratory. All of this material was then grouped in two month intervals in the two combinations which are possible (chart 4).

As is to be expected, there is some variation from period to period, but it is by far too slight when measured by ϵ_M to warrant the conclusion that it is related to seasonal conditions. The nature of the variations and their interrelationships in the two groupings, when corresponding periods of the year are compared, would bear out this conclusion. The observations, however, were not made for this specific purpose, and perhaps it may be best to leave the question open for the time being, remembering only that as it stands our evidence cannot be interpreted as indicating seasonal variation in the sugar of the blood of rabbits which are confined in the laboratory.

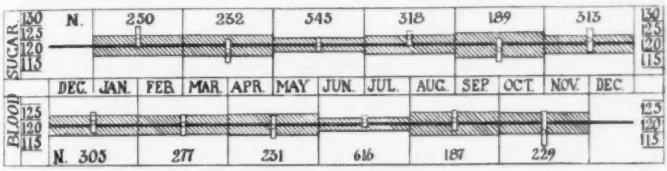

Chart 4.—Seasonal variation of the blood sugar of the rabbit; 1,847 observations distributed as indicated in the chart.

DIURNAL VARIATION

Diurnal variation is also an important consideration in practical experimental work as well as of considerable interest in itself. Can it be presumed that, other things being equal, the blood sugar level is independent of the time of day? This problem has been attacked by various authors, notably by Eadie,[5] and usually answered in the affirmative. It was early noted by Macleod,[6] later by Eadie as well as by others, that when specimens of blood are taken at short intervals, there is frequently a marked variation in the sugar content from specimen to specimen.

Since time progresses as the observations are accumulated, a progressive change in the blood sugar level may be and often has been interpreted as a diurnal phenomenon. Such a progressive change, however, might just as well be associated with the effect on the animal of

5. Eadie, G. S.: Am. J. Physiol. **63**:513 (Feb.) 1923.
6. Macleod, J. J. R.: Am. J. Physiol. **38**:415, 1915.

TABLE 4.—*Results for Determination of Diurnal Variation* *

Rabbit	Sex	Body Weight		Blood Sugar									Characteristics of the "Individual" Series		
		Initial	Final	9 A.M.	10 A.M.	11 A.M	12 M.	1 P.M.	2 P.M.	3 P.M.	4 P.M.	5 P.M.	M	ϵ	ϵ_M
270	M	2.36	2.23	110	137	130	126	113	123	141	129	131			
				134	121	144	139	145	129	129	110	131			
				155	134	118	131	121	113	129	126	136	129	11.3	2.2
271	F	3.03	3.66	115	121	116	113	112	110	109	130	110			
				136	107	139	136	129	121	123	141	118			
				139	134	121	123	139	126	126	121	131	124	10.5	2.0
273	M	2.59	2.70	149	118	119	118	97	94	123	122	127			
				121	117	110	126	129	123	131	126	121			
				136	126	123	118	126	121	121	129	131	122	10.6	2.0
275	F	2.97	3.60	140	122	130	131	122	90	123	131	140			
				118	127	113	132	120	121	129	129	118			
				129	123	126	113	121	121	129	136	121	124	8.7	1.7
277	F	2.35	2.60	129	142	126	113	118	121	110	136	131			
				121	121	136	139	118	123	118	121	123	125	9.0	1.9
279	F	2.30	2.24	121	121	121	134	126	118	118	116	130			
				123	129	101	106	125	126	129	129	139	123	8.5	2.0
281	M	1.85	2.31	110	131	104	130	121	141	126	139	123			
				107	131	129	123	136	126	134	136	121			
				123	123	129	129	134	129	131	139	123	127	9.1	1.8
286	M	2.44	2.54	116	121	107	118	113	130	129	126	141			
				113	118	113	118	123	126	132	121	134			
				116	123	121	123	131	119	123	136	118	123	7.8	1.5
288	F	2.42	2.06	123	136	121	109	106	117	123	121	113			
				110	123	107	116	126	121	123	126	113			
				113	121	121	116	118	139	113	121	129	119	7.9	1.5
292	M	2.15	1.80	102	113	134	118	113	129	113	141	131			
				126	122	134	132	121	105	118	139	118	123	11.3	2.7
294	M	2.15	2.61	124	105	140	120	118	116	136	124	127			
				131	113	129	135	134	141	129	113	126			
				121	131	139	131	118	131	123	129	126	126	9.0	1.7
295	M	2.15	2.23	121	121	117	136	118	121	118	129	134	124	7.2	2.4
296	M	2.67	2.56	118	126	131	135	116	123	118	126	132			
				131	127	126	126	131	123	118	131	127			
				118	118	123	129	126	123	113	126	131	125	5.6	1.1
297	F	2.37	2.21	97	106	123	136	131	118	123	117	131			
				125	118	116	118	129	123	110	125	133	121	9.8	2.3
298	M	2.36	2.02	106	130	131	129	129	129	121	102	129			
				134	110	123	134	119	139	116	110	129			
				131	121	113	121	129	118	139	118	134	124	9.0	1.9
299	M	2.36	2.34	117	106	113	107	117	118	115	113	123			
				134	113	123	131	126	129	113	116	123			
				129	121	134	116	131	131	123	126	129	121	8.1	1.6
300	M	2.20	1.60	121	119	107	129	124	118	114	107	121			
				103	110	130	118	121	129	123	118	123			
				126	118	118	121	126	136	118	118	121	120	6.5	1.2
301	M	1.66	1.53	139	139	124	129	113	134	118	132	116	127	7.3	2.4
302	M	2.55	2.45	97	118	121	121	129	131	131	139	118			
				129	131	136	126	134	121	136	139	121	127	10.2	2.4
203	M	2.10	2.25	113	129	123	130	118	131	123	126	129			
				123	121	126	118	129	139	126	123	121	125	5.9	1.4
205	?	2.37	2.35	131	126	123	131	131	121	136	131	134	129	5.0	1.7
Characteristics of Series by Hours															
M				123	123	123	125	124	124	123	124	125			
ϵ				12	8	10	8	10	9	6	10	5			
ϵ_M				1.7	1.2	1.4	1.2	1.2	1.3	0.9	1.4	0.7			

* In the table there were 459 observations; M = 124; ϵ = 9.1; ϵ_M = 4.2.

drawing the specimens, the hemorrhage glycemia of the older authors (Scott [7]). This phenomenon is illustrated in chart 6 and table 5.

To determine whether or not there is a diurnal variation and at the same time to avoid any possible effects from taking consecutive specimens, the following experiment was devised. Fifty-one determinations were made at each hour of the working day, that is, from 9:00 a. m. to 5:00 p. m., inclusive. An equal number of determinations was made on a given animal at each hour. The rabbits were fed ad lib to one hour before the specimens of blood were drawn. Water was allowed at all times. Only one specimen was drawn from any particular rabbit on a given day. The results are shown in table 4.

From this table it appears that when the other conditions are maintained in as constant a condition as is practical, the blood sugar

TABLE 5.—*Observations on Diurnal Variations at Two Hour Intervals for Twenty-Four Hours*

	Blood Sugar												Characteristics of Series by Individuals		
	A. M.						P. M.								
Rabbit	1	3	5	7	9	11	1	3	5	7	9	11	M	ϵ	ϵ_M
68.....	147	138	160	170	151	160	122	136	157	156	157	141	150	13.3	3.8
74.....	125	154	156	125	140	151	137	125	148	150	149	147	142	11.6	3.4
79.....	122	132	141	112	142	140	143	142	151	148	142	134	137	11.0	3.2
80.....	129	120	117	116	138	140	122	135	140	130	136	133	130	8.9	2.6
82.....	125	138	128	122	144	130	145	141	124	113	114	137	130	11.0	3.2
83.....	154	154	150	140	135	146	138	157	156	159	141	154	149	8.3	2.4
84.....	155	154	148	133	125	138	128	138	140	136	128	162	140	11.9	3.4
85.....	152	138	130	127	125	125	134	135	134	140	126	129	132	5.9	1.7
Characteristics of Series by Hours															
M.....	137	141	141	131	138	141	134	139	144	141	137	142			
ϵ.....	14	12	15	15	9	11	8	9	11	15	14	11			
ϵ_M....	4.8	4.3	5.2	5.4	3.2	4.0	2.7	3.2	4.0	5.4	4.8	3.9			

level in the rabbit is independent of the time of day, at least during the ordinary working hours.

Some years ago a short series of observations was made at two hour intervals throughout the twenty-four hours. The series is not sufficiently long to warrant conclusions, but it does not seem probable that the opportunity of making a really adequate series will occur soon. The data are therefore offered in table 5 at their face value and without comment except that they seem to be in harmony with the conclusion stated. These animals had access to food and water throughout the period of observation.

THE CONSTITUTION OF THE GROUP OF SUBJECTS

Animals have been found to vary among themselves in every character which has been studied from the point of view of such varia-

7. Scott, E. L.: Am. J. Physiol. **34**:271, 1914.

tions. There is no *a priori* reason to suppose that the characteristic blood sugar level is an exception to this rule. If the blood sugar level is not an exception, it would follow that a group of observations made on a single animal could not have as great a general significance as would the same number of observations each of which was made on a different animal. On the other hand, it might be expected that the series made on one animal would have the higher precision.

This was tested in various ways. Approximately 100 observations were made on each of three rabbits from about Dec. 1, 1924, to April 1, 1925, not more than one observation being made on any one day. These three series should be compared with another series (chart 5); they were made at about the same time, and the number of observations and subjects were equal.

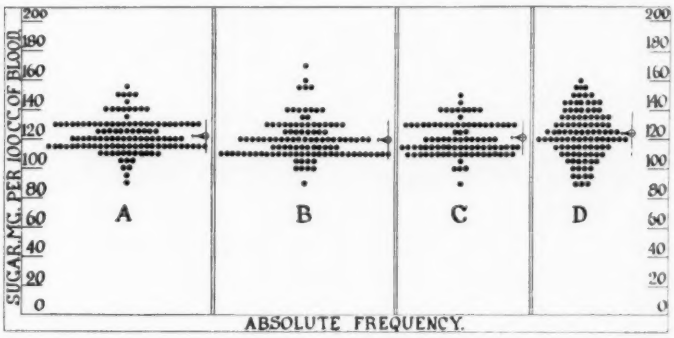

Chart 5.—A study of the blood sugar of rabbits. The three series of many observations on one animal (A, B and C) should be compared with one series (D) of one observation on each of many animals. A, 117 observation on rabbit 84, made between Nov. 21, 1923, and April 1, 1924; B, 112 observations on rabbit 88, made between November 26 and April 1 of the same years; C, 92 observations on rabbit 94, made between December 7 and April 1 of the same years; D, 104 observations on 104 subjects made between November, 1923, and November, 1926. These observations were selected in such a manner that their value was without influence on the selection.

It is seen that a slight gain in precision is shown by the series which were derived from a single animal, but the gain is hardly of sufficient magnitude to be of practical value in drawing conclusions; ϵ_M, for the "individual" series, being 1.2, 1.4 and 1.1 respectively, while for the heterogeneous series it was 1.6. Scott [3] gave 13.2 as the mean value of ϵ for ten series of this number of observations made on heterogeneous groups of animals from which the mean value of ϵ_M would be 1.3. The mean ϵ_M for the foregoing three series is 1.2.

In the first series studied in the section on diurnal variation (table 4), twenty-seven observations were made on each of twelve animals. For the twelve animals, the mean value for ϵ is 8.8 while that for the nine series of fifty-one observations is 8.6. Strictly interpreted, this would mean that there was actually a greater variation among the specimens taken wholly from a single animal than there was in the specimens taken from the mixed groups. The difference, however, is too slight to justify such a conclusion. In any case, the data do not encourage one to expect any great gain in precision by the use of a single animal.

The means for the three rabbits studied in chart 5 do not differ significantly from those of an equal number of observations on a group of rabbits and so give no indications of the existence of a characteristic blood sugar level. Those shown in table 4, however, are not so consistent. In this table the means of the mixed groups (vertical columns) are remarkably similar while those for the individual animals (horizontal lines) show considerable variation. The same condition is shown in another group in table 5. The number of observations made, as shown in tables 4 and 5, is not so great as one would wish, but taken altogether the data appear to indicate that there are characteristic individual blood sugar levels which differ sufficiently to render data derived from different animals uncomparable and so vitiate conclusions based on such material unless the effect of the experimental condition is considerable.

Since a marked gain in precision cannot be expected by confining the observations to a single animal it would seem to be the better practice to include as many animals in the series as possible. The ideal would be to have the number of animals and observations equal (Pierce and Scott [8]).

CONTROL SERIES

All experiments should be accompanied by control observations which should be so made as to show the presumable behavior of the animal under the conditions which have been chosen as the standard and with which the response to the experimental conditions is to be compared. In studies on the blood sugar curve the usual practice is to make an initial observation just before the administration of the substance—insulin, dextrose, or what not—the effect of which is being studied. Is the initial observation of itself an adequate control? Can it be presumed that the second, third or fourth specimen would have been the same as the first had insulin, for instance, not been injected. Is it possible that the process of taking specimens or simply of the lapse of time might affect the result? Such an effect might be brought about

8. Pierce, H. F., and Scott, E. L.: Variation in Reducing Power (Sugar) of Normal Human Blood, Arch. Int. Med. **41**:586 (April) 1928.

through excitement, discomfort or loss of blood to say nothing of less obvious factors (Scott [7]). If such an effect exists, the apparent reaction to the factor being studied might be masked or exaggerated depending on whether the two factors act in the same or opposite directions.

Fifty observations were made in order to test this hypothesis. In those observations the amount of 0.9 per cent of sodium chloride solution, which was used to carry 1 unit of insulin per kilogram of body weight but which, in this study, did not contain insulin, was injected into the animals. Observations were then made three-quarters, one and a half, two and a half and three and a half hours after the injection. The results are shown in chart 6.

It will be noticed that there is a slight progressive rise as the number of specimens is increased. This rise was noted previously by Scott and Ford [9] for rabbits, and for dogs by Hastings and Scott.[10] It is true that the rise is not great and that possibly it may be neglected for

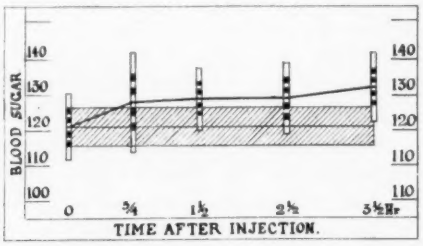

Chart 6.—Experiment to show the effect of taking successive specimens of blood observed on the blood sugar.

much work, but it should be noted that in every case it is significant as judged by Scott's [3] criteria, and it may be sufficient to explain the occasional apparent lack of effect of exceptionally small doses of insulin.

In certain types of experiments it may be desirable to make the control observations at a time somewhat removed from the observations made under the experimental conditions. Is such a practice justifiable? It has been shown that the variations exhibited by one animal may be as great as are those shown in a group of animals (tables 4 and 6). It follows from this that the blood sugar level of one animal cannot be considered to be constant from day to day. It has also been shown (table 5 and chart 6; Macleod,[6] Eadie [5]) that similar variations occur from hour to hour. In table 6 are shown the results in three groups of series. In the first two groups three observations were made on each rabbit of a

9. Scott, E. L., and Ford, T. H.: Am. J. Physiol. **63**:520 (Feb.) 1923.

10. Hastings, A. B., and Scott, E. L.: Proc. Soc. Exper. Biol. & Med. **17**:120, 1920.

heterogeneous lot of fifty. In the third group six observations were made on each animal of a similar lot. The observations were then arranged in series, one observation on each animal appearing in each series. The first series for each lot contained the earliest observation

TABLE 6.—*Observations on the Possibility of Individual Characteristics in Different Animals*

A				B				C						
	Blood Sugar				Blood Sugar				Blood Sugar					
Rabbit	1	2	3	Rabbit	1	2	3	Rabbit	1	2	3	4	5	6
14....	138	128	154	71....	115	121	116	118....	99	120	115	139	152	148
16....	134	134	142	75....	122	130	131	121....	142	138	115	148	145	143
17....	116	119	130	77....	126	113	118	124....	123	120	117	134	97	126
27....	112	122	122	148....	99	138	105	125....	143	126	113	141	134	129
25....	112	112	122	149....	112	114	125	126....	141	108	176	141	148	143
26....	116	105	116	150....	105	128	130	127....	134	115	132	119	138	134
28....	-122	145	128	151....	99	119	130	134....	123	129	104	129	129	129
33....	128	145	128	152....	102	135	132	136....	-100	120	110	134	157	120
34....	148	122	128	153....	130	114	132	137....	145	101	110	117	138	145
35....	132	112	122	154....	125	135	119	138....	123	129	117	98	148	143
37....	128	119	119	158....	134	129	139	144....	99	129	132	138	117	117
39....	116	108	125	161....	136	118	126	145....	134	132	123	119	138	143
44....	138	122	122	162....	149	105	108	146....	115	123	129	132	123	129
70....	110	116	110	163....	-131	147	113	147....	115	122	123	132	120	134
72....	124	144	108	165....	121	134	113	148....	104	141	110	143	141	132
74....	105	116	90	166....	144	136	120	149....	117	119	129	129	123	132
77....	122	142	105	167....	131	107	105	150....	110	132	134	129	134	123
79....	110	108	128	168....	129	118	118	151....	104	123	134	145	141	123
81....	145	160	170	169....	134	118	128	152....	107	138	135	132	126	113
82....	133	114	118	170....	126	136	129	153....	134	119	110	135	145	135
83....	126	132	122	172....	126	131	102	158....	139	121	134	121	121	123
84....	132	145	132	174....	116	118	105	162....	149	105	108	121	118	123
85....	161	147	142	176....	99	113	131	163....	147	113	121	134	126	136
86....	142	146	145	177....	123	121	134	166....	144	130	120	118	136	129
94....	125	114	110	178....	134	121	123	167....	107	105	129	116	110	123
116....	130	168	160	179....	116	121	134	168....	129	113	134	118	128	126
117....	138	160	170	180....	123	129	118	182....	105	110	113	116	129	107
118....	128	156	167	182....	105	110	123	185....	121	107	131	136	131	116
119....	154	130	116	183....	116	105	130	194....	116	131	121	116	94	110
120....	138	116	112	185....	131	121	107	207....	126	107	105	118	118	136
121	128	151	151	189....	113	118	107	218....	139	105	105	94	90	99
124....	116	125	116	190....	121	111	107	221....	134	105	121	94	97	105
125....	112	125	122	191....	118	126	107	223....	116	118	97	105	94	97
126....	128	112	128	193....	107	136	110	270....	110	137	130	126	113	123
127....	114	110	119	200....	99	107	116	271....	115	121	116	113	112	110
128....	108	128	125	201....	121	116	94	273....	118	119	118	97	94	123
130....	105	116	122	202....	118	105	131	275....	122	130	131	122	99	123
132....	142	160	128	204....	105	113	105	277....	126	113	118	121	110	136
134....	116	119	130	207....	129	107	105	279....	129	134	126	118	118	116
135....	119	116	128	208....	113	97	89	281....	130	121	141	126	130	123
136....	157	115	105	209....	126	99	134	286....	118	113	130	129	126	141
137....	142	90	128	214....	99	99	116	288....	116	117	123	121	113	123
138....	119	125	96	217....	123	126	102	290....	129	130	134	126	110	119
139....	119	130	114	218....	139	105	105	292....	129	113	141	131	102	113
141....	125	128	130	221....	134	105	121	294....	116	136	124	127	124	105
142....	94	119	99	223....	116	118	97	295....	118	129	134	121	121	117
144....	94	122	128	228....	110	110	99	299....	118	120	132	118	126	131
145....	130	128	119	229....	113	105	102	297....	117	131	97	106	125	136
146....	110	119	125	230....	131	116	110	298....	102	129	106	130	131	129
147....	110	128	119	270....	110	137	130	299....	123	117	106	113	107	117
M	125	128	126		120	124	127		124	123	127	124	123	123
σ	15	16	17		12	16	17		14	12	12	13	16	12
ϵ_M	2.1	2.2	2.4		1.8	2.2	2.4		2.0	1.7	1.8	1.8	2.3	1.8

on the respective rabbits; the second series, the next consecutive observation, and so on through the group. There was no further selection of the observations. These groups are presented to show that while there may be considerable variation in the blood sugar level of the individual animals from day to day, the mean level of the group as a whole is

relatively stable (Pierce and Scott [8]). From this it would appear that one may presume the mean blood sugar level of an adequate series of observations made on a group of animals to be approximately constant from day to day and that, under these circumstances, the experimental observations need not follow the control observations immediately.

It sometimes even occurs that it is undesirable or impossible to use the same animals for the control and experimental observations. Figure 10 in the paper by Scott [3] illustrated the range within which the means of series of various lengths may be expected to fall. When the effect of the experimental conditions is sufficient to throw the results widely outside of this range, conclusions may be drawn from such controls with the indicated degree of precision and without obvious objection. It should be evident, however, that the experimental effect must be of considerable magnitude and that the conclusions must be distinctly guarded in their quantitative aspects.

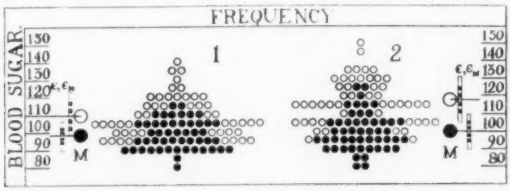

Chart 7.—Two series to show the effect of a short period of inanition on the level and variability of the blood sugar of rabbits. 1, the initials of series A, circles and after inanition..., dots; 2, the initials of series B..., circles, and after inanition..., dots. Circles, rabbits fed ad lib.; dots, blood sugar after eighteen hours inanition. Total length of bars $\pm\epsilon$, shaded portion $\pm\epsilon m$.

INANITION

There is apparently a widely accepted agreement among workers in this field that a short period of inanition just previous to the drawing of the speciman of blood markedly increases the precision of the estimations on the blood sugar. We sought to test this by the following experiments. In the first there were two groups of fifty observations each. In each group there were two series, in the first of which the animals received their accustomed food ad lib. to the time of taking the specimen of blood; in the second series they were subjected to a period of eighteen hours inanition before the specimen was drawn. The animals in one of these groups show rather low values in the series in which they were fed and this possibly may be related to the fact that there was some infection in this group of animals because of wounds which they had inflicted on one another in fighting, though the change is contrary in direction to that usually associated with infection. While

this undoubtedly may affect the value of the series as a study of the effects of inanition on the level of the sugar, it is not obvious that it would affect the variability, and so the series is included. From chart 7 it will be seen that inanition in both groups is accompanied by a distinct drop in the blood sugar level and that this drop is accompanied in each case by an increased precision as indicated by ϵ.

In another experiment we sought to study the progressive effect of inanition over a period of twenty-four hours. These observations were made by a team of observers working in eight hour shifts, and the results are consequently open to some objection, owing to the variable personal equations of the observers. The effect of taking successive specimens is also a factor that should probably be considered. All in all the design of the experiment is not of the best, but as there is little

TABLE 7.—*The Progressive Effect of Inanition on Blood Sugar During Twenty-Four Hours*

	Elapsed Time in Hours												
Rabbit	0	2	4	6	8	10	12	14	16	18	20	22	24
264.....	138	124	140	121	116	134	106	114	141	131	106	114	117
265.....	120	137	113	129	113	117	115	108	104	112	112	112	112
274.....	132	140	134	129	134	115	109	107	116	131	113	128	105
268.....	141	142	116	112	112	108	110	120	130	128	114	110	114
279.....	140	127	102	124	112	105	116	124	124	134	119	121	116
280.....	118	119	126	106	92	105	111	119	124	117	116	118	122
281.....	132	128	128	133	128	128	124	118	117	117	113	132	114
282.....	168	144	141	134	122	128	118	120	114	110	113	112	114
283.....	168	142	142	131	131	125	129	122	125	119	122	125	127
284.....	132	130	122	114	159	116	117	136	112	114	120	117	108
285.....	135	142	122	138	135	122	119	117	122	118	125	118	120
286.....	138	122	151	114	119	114	113	115	109	108	107	108	
M.....	138	133	128	124	123	118	116	118	120	120	115	118	115
ϵ.....	16	9	14	10	17	10	6	6	11	9	8	7	6
ϵ_M.....	4.5	2.6	4.1	3.0	4.8	2.8	1.7	1.6	3.1	2.5	1.6	2.1	1.8

probability that the series will be carried to greater length in this form the data are given for what they are worth. In a general way they may be taken to indicate that the maximum precision is attained after about ten hours' inanition and that when once reached this precision is not much changed during the following fourteen hours. Apparently, the blood sugar level follows about the same time relations, reaching its minimum at about ten hours, and is approximately constant from then to the end of the period studied.

Thus, the practice of subjecting the animals to a brief period of inanition with the purpose of increasing the precision of the results seems to be justified in the case of rabbits. Some unpublished work in our laboratory indicates just as conclusively that with cats and rats the reverse condition holds, the greatest precision in these species being obtained with animals that have been fed. When the animals are subjected to inanition, it must be borne in mind that the observations were made under a special condition which cannot be called normal (usual)

and that conclusions based on such observations will have a correspondingly limited application. There is no evident reason why the practice of subjecting the animals to a short period of inanition should not be followed in the assay of insulin. Whether or not such a practice is permissible in other studies will depend on the object of the particular research. In any case the legitimacy of the practice is open to question and when used its justification is necessarily an integral part of the research.

SUMMARY

1. For a series of 1,625 observations, the mean reducing power (blood sugar) of rabbits that had been fed was found to be 123 mg. per hundred cubic centimeters of blood with a mean deviation of 13. Some of the conditions which are or may be correlated with deviations in the reducing power of the blood and which possibly may lead to erroneous conclusions are discussed and illustrated.

2. The blood sugar seems to be independent of age, weight or sex, within the precision of the methods used.

3. It is probable that the reducing power of the blood of the rabbit is independent of the time of year provided that the animals are housed in the laboratory.

4. It also seems to be independent of the time of day.

5. It may be affected by the long continued use of the animals for such studies.

6. The use of many subjects in a research makes the general application of the conclusions based on the results more probable. On the other hand, many observations made on a single subject do not have a significantly greater precision and the research loses something of its general significance.

7. Some of the principles which determine a significant control were studied and methods for establishing such a control are discussed.

8. A short period of inanition causes a slight drop in the reducing power of the blood of the rabbit and rat. The variability of the results is decreased somewhat in the rabbit, while it is increased in the rat and cat.

PANCREATIC FUNCTION

III. THE PANCREATIC SECRETION IN DISTURBED GASTRIC SECRETION *

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Since the investigations of Pavlov and his associates [1] in 1878, the mechanism of the pancreatic secretion has become of general interest. Pavlov reported that the pancreatic secretion is promoted by the entrance of the acid chyme into the duodenum, and not by the presence of that in the stomach. This stimulation of the secretion depends largely on the acidity of the chyme, for if a solution of 0.4 per cent hydrochloric acid is introduced into the stomach and rapidly discharged into the duodenum, a copious secretion of the pancreatic juice follows.

Popielski [2] and, independently, Wertheimer and Lepage [3] proved that even when all the secretory nerves of the pancreas are severed, the pancreatic secretion is promoted by acid. Popielski attributed this to a reflex, the center of which lies in the pancreas.

The classic experiments of Bayliss and Starling [4] showed in a striking way that in the action of dilute acid on the duodenal mucosa a substance, secretin, is formed, which can accelerate the flow of pancreatic juice even when all nervous connections with the secretory gland are severed. Starling further pointed out that, whereas in the mouth the reaction, which must be rapid, is entirely nervous, in the stomach the nervous mechanism is combined with the more primitive chemical mechanism. The nervous secretion preponderates in this viscus. He added further that in regard to the pancreas, the primitive chemical

* Submitted for publication, Oct. 31, 1928.

* From the medical clinic of Prof. R. Inada, Imperial University of Tokyo.

1. Afanassiew, M., and Pawlow, J.: Beiträge zur Physiologie des Pancreas, Arch. f. d. ges. Physiol. **16**:173, 1878. Pawlow, J.: Weitere Beiträge zur Physiologie der Bauchspeicheldrüse, ibid. **17**:555, 1878.

2. Popielski, L. B.: Ueber die sekretionshemmenden Nerven des Pankreas, Dissertation, 1896, cited by Baylina.

3. Wertheimer, E., and Lepage, L.: Sécretion pancreatique et atropine, Comp. rend. Soc. de biol., 1901, p. 759.

4. Bayliss, W. M., and Starling, E. H.: The Mechanism of Pancreatic Secretion, J. Physiol. **28**:325, 1902.

mechanism, namely, the formation of hormones and their circulation through the blood to the reactive tissue, suffices to account for the whole activity of the gland, and it is doubtful whether the nervous system plays any part in this activity.

Pavlov and Fleig,[5] as well as Cohnheim and Klee,[6] proved that soap also is a vigorous stimulator of the flow of pancreatic juice. Baylina [7] insisted that two mechanisms of pancreatic secretion exist, namely, chemical and nervous. Cohnheim and Klee proved that the administration of food itself stimulates the flow of pancreatic juice and bile similarly to the nervous stimulation of the stomach.

The estimation of the enzymatic activity opened a new era. In 1889, Boas asserted that the pancreatic juice is often detected in the stomach. Boldyreff [8] found that when oil is introduced into the stomach of dogs, a copious amount of the duodenal contents dashes into the stomach. In 86 per cent of his cases, Volhard [9] detected trypsin in the fluid removed from the stomach thirty minutes after the introduction of 200 cc. of oil, while Faubel [10] was able to detect it in but 70.6 per cent.

Ehrmann and Lederer [11] collected the contents of the stomach forty-five minutes after the introduction of olive oil through a tube into the stomach and estimated the tryptic activity of the fluid separated under the oil. They found that in cases of achylia gastrica or in achlorhydria the tryptic activity is not only not diminished but in some cases is rather increased in comparison with that found in cases showing normal acidity.

Frank and Schittenhelm [12] also found trypsin in the regurgitation fluids in cases of achylia gastrica after oil was introduced.

Okada,[13] using the duodenal tube and estimating the tryptic activity of the duodenal return with the casein method, definitely proved for the

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5. Fleig, C.: Arch. gén. de méd. **1**:1473, 1903.

6. Cohnheim, O., and Klee, P.: Zur Physiologie des Pankreas, Ztschr. f. physiol. Chem. **78**:464, 1912.

7. Baylina, A.: Normale Pankreassekretion als Synthese von nervösen und humoralen Einfluss, Arch. f. d. ges. Physiol. **142**:531, 1911.

8. Boldyreff, W.: Der Uebertritt des natürlichen Gemisches aus Pankreassaft, Darmsaft und Galle in den Magen, Arch. f. d. ges. Physiol. **121**:13, 1907.

9. Volhard, F.: Ueber die Untersuchung des Pankreassaftes beim Menschen und eine Methode der quantitativen Trypsinbestimmung, München. med. Wchnschr. **54**:403, 1907.

10. Faubel, O.: Untersuchungen über den menschlichen Bauchspeichel und das Fermentgesetzdes Trypsins, Hofm. Beitr. **10**:35, 1907.

11. Ehrmann, R., and Lederer, R.: Ueber das Verhalten des Pankreas bei Achylia und Anazidität des Magens, Deutsche med. Wchnschr. **35**:879, 1909.

12. Frank, F., and Schittenhelm, A.: Vorkommen und Nachweis von Trypsin und Erepsin im Magen-Darmkanal, Ztschr. f. exper. Path. u. Therap. **8**:237, 1911.

13. Okada, S.: Ueber die Pankreassekretion bei Sekretionsstörungen des Magens, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **13**:143, 1914.

first time that the flow of pancreatic juice is not necessarily unfavorably affected by disturbance of the gastric secretion, but rather that it is even accelerated in some cases.

Using the same method as Okada and, in addition, estimating diastase following the procedure of Wohlgemuth, Hatta and Marui [14] also proved that the pancreatic secretion is not necessarily disturbed by disturbed gastric secretion.

After investigations of the duodenal juice in subjects with disturbed gastric secretion the conclusions of Schoppe,[15] Isaac-Krieger,[16] Katsch and von Friedrich,[17] Roth and Sternberg,[18] Schoening,[19] Deloch,[20] McClure and his associates,[21] Nagai,[22] Kusnetzow and Michailowa [23] and others agreed in the main with those of Okada. It was pointed out, however, that the methods hitherto applied, i.e., the estimation of the enzymatic activity of the duodenal return, encountered theoretical as well as real objections when quantitative tests were considered. The presence of a considerable amount of saliva, gastric juice and biliary secretion so diluted the duodenal contents that a correct quantitative study of the pancreatic ferments was impossible. We have devised a

14. Hatta, Z., and Marui, K.: Ueber die Tätigkeit der Bauchspeicheldrüsen bei den Verdauungsstörungen des Magens sowie bei Aufnahme verschiedener Nahrungsstoffe und Arzneimittel, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **20**:121, 1918.

15. Schoppe, W.: Vergleichende Untersuchungen auf tryptisches Ferment in den Fäces und im Duodenalsaft mit der Casein-Methode, Arch. Verdauungskr. **28**:289, 1922.

16. Isaac-Krieger, K.: Welchen Wert hat zurzeit die Untersuchung des Duodenalsaftes für die Diagnose der Darmkrankheiten? Med. Klin. **18**:431, 1922.

17. Katsch, G., and von Friedrich, L.: Bauchspeichelfluss auf Aetherreiz, Klin. Wchnschr. **1**:112, 1922.

18. Roth, N., and Sternberg, F.: Zur Frage der Pankreasachylie, Deutsche med. Wchnschr. **48**:1207, 1922.

19. Schoening, 1922, cited by Roth and Sternberg (footnote 18).

20. Deloch, E.: Zur Funktionsprüfung der äusseren Pankreassekretion durch Untersuchung des Duodenalsaftes, Arch. Verdauungskr. **30**:27, 1922.

21. McClure, C. W., and Wetmore, A. S.: Studies in Pancreatic Function: Enzyme Concentration of Duodenal Contents After Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men, Boston M. & S. J. **187**:882, 1922. McClure, C. W., and Jones, C. M.: Studies in Pancreatic Function: The Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving the Pancreas, Liver and Stomach, ibid. **187**:909, 1922; Pancreatic Secretion in Man, Editorial, J. A. M. A. **80**:1145 (April 21) 1923.

22. Nagai, K.: On the Pancreatic Secretion in Achlorhydria Gastrica, Nippon Naika Gakkai Zasshi **10**:1211, 1923.

23. Kusnetzow, N. W., and Michailowa, S. J.: Die Sekretionstätigkeit der Bauchspeicheldrüse im Verlaufe von Erkrankungen der Digestionsorgane, Arch. Verdauungskr. **40**:41, 1927.

new method (published in the first paper of this series [24]) which affords a reliable and accurate estimation of pancreatic function. Therefore, it might not be amiss to investigate this interesting problem further.

CLINICAL MATERIAL

The cases under consideration consist of an unselected group of seven cases of achylia gastrica and five cases of cancer of the stomach in connection with achlorhydria. Nine of the patients were men and three women. The cases of achylia gastrica were complicated by cholelithiasis, bronchial asthma, cardialgia and mild beriberi. In a woman, aged 29, with cancer of the stomach, the peritoneal cavity was involved with metastases and effusion. The scanty secretion and low enzymatic activity in this case were probably due to the extremely prostrated condition of the patient or to pancreatic involvement.

METHOD

The method employed in this investigation is the same as that described in the first paper of this series.

The results in three hour specimens of the duodenal contents shown in table 1 are presented in table 2.

In case 2 all of the enzymes as well as the bile pigment were extremely diminished, owing to the scanty amount of the juice obtained. In this case the achylia gastrica was complicated by peritoneal carcinosis with effusion, and the patient was extremely emaciated and prostrated; hence, the disturbed secretion of the pancreatic juice might be regarded as the consequence of this unusual condition. From the foregoing case, it is evident that the majority of cases of achylia gastrica and cancer of the stomach complicated by achlorhydria show normal enzymatic activity in the duodenal return; in some cases it is increased, so that the general average is higher than that in normal cases with undisturbed gastric secretion (we considered as a normal average 70 kilo-units for trypsin, 140 kilo-units for amylase and lipase in the first paper of this series). The average of bile pigment is also high, but it must be taken into consideration that most patients examined here were relatively old (eight were over 40 years of age). We found (as reported in the first paper) that the elimination of bile pigment increases with age.

In a study of the enzymatic activity, using the highest degrees found in frequent half-hourly or hourly determinations during three hours, we also found normal values in the main.

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24. Okada, S.; Sakurai, E.; Imazu, T., and Kuramochi, K.: Pancreatic Function: I. The Quantitative Estimation of Pancreatic Secretion, Arch. Int. Med. **42**:270 (Aug.) 1928.

TABLE 1.—*General Survey of the Data*

Case and Name	Sex and Age	Date	Stimulants Introduced into the Duodenum	Amount of Duodenal Return in Three Hours, Cc.	Degree of Enzymatic Activity									Trypsin in Three Hours Kilounit	Amylase in Three Hours Kilounit	Lipase in Three Hours Kilounit	Bile Pigment in Three Hours, Mg.	Gastric Juice		Comment
					Trypsin			Amylase			Lipase							Free Hydrochloric Acid	Total Acidity	
					1 Hour Unit	2 Hour Unit	3 Hour Unit	1 Hour Unit	2 Hour Unit	3 Hour Unit	1 Hour Unit	2 Hour Unit	3 Hour Unit							
1 K. W.	♂ 41	1/15/27	Alcohol	129.5	320	320	800	893	811	1,763	678	780	760	60.6	148.2	93.2	17.3	0	10	Achylia gastrica + cholelithiasis
		1/19/27	Water	97.0	320	500	500	527	896	979	726	810	1,164	55.6	134.7	87.1	7.6			
		1/22/27	HCl (0.2%)	172.5	200	200	500	907	636	1,260	410	560	500	61.7	164.7	109.4	26.6			
		2/ 1/27	Ether	196.0	320	200	320	908	603	926	508	440	396	58.9	170.7	90.0	30.4			
2 Y. T.	♀ 41	1/28/27	HCl (0.2%)	137.5	320	500	500	1,243	2,203	2,162	1,260	516	468	53.4	220.8	140.8	19.3	0	13	Achylia gastrica
		2/ 2/27	Water	107.0	800	500	320	1,885	2,287	1,873	700	360	456	65.7	202.6	61.5	9.7			
3 K. W.	♂ 20	3/19/27	No	104.5	800	320	500	2,124	2,053	1,987	2,112	1,020	1,428	67.5	223.0	165.8	10.7	0	5	Achylia gastrica
		4/26/27	No	119.5	800	500	1,250	1,851	2,284	2,609	1,776	696	3,520							
					500	1,250	320	1,476	1,740	1,790	1,610	2,480	342	85.2	189.5	248.3	35.1			
					800	320	500	1,557	1,819	1,880	3,220	1,150	780							
4 I. T.	♂ 20	8/30/27	Water	159.0	250	1,000	1,000	637	1,663	1,598	476	900	1,390	126.8	217.1	163.2	19.5	0	8	Achylia gastrica + beriberi
5 K. O.	♂ 54	9/ 3/27	Water	196.0	320	320	320	918	1,085	804	1,900	1,100	1,400	62.8	185.7	272.6	23.6	0	8	Achylia gastrica + cholelithiasis
6 H. K.	♂ 34	1/13/28	No	80.0	250	800	800	2,185	1,122	2,036	58	420	142	65.5	129.3	30.9	15.5	0	16	Achylia gastrica + bronchial asthma
					500	800	320	2,119	1,867	2,230	138	144	115							
7 M. T.	♀ 61	1/25/28	No	88.0	320	250	500	1,221	1,659	1,543	1,188	262	1,210	36.4	128.6	95.8	5.3	0	7	Achylia gastrica + cardialgia
8 M. W.	♂ 49	12/24/26	Alcohol	105.0	800	1,250	1,250	1,921	2,043	1,829	255	540	1,025	122.1	208.2	449.2	27.2	0	12	Cancer of the stomach
					800	1,250	2,000	2,083	1,979	2,188	575	420	960							
9 Y. O.	♂ 54	3/ 5/27	Water	148.0	500	800	800	1,238	2,018	2,067	1,790	4,960	2,640	101.9	257.9	467.8	20.4	0	8	Cancer of the stomach
10 K. I.	♂ 64	12/ 6/27	Water	196.5	50	500	800	984	1,810	1,833	185	1,560	1,775	63.9	286.1	198.1	11.9	0	10	Cancer of the stomach
					200	500	500	1,133	2,197	1,694	680	1,860	1,000							
11 K. A.	♀ 29	12/23/27	No	15.0	800	500	500	2,530	1,859	1,740	230	170	110	9.5	52.0	3.4	0.5	0	12	Cancer of the stomach + peritoneal carcinosis
12 K. I.	♂ 62	4/13/28	No	203.0	500	500	500	1,305	2,746	2,601	936	965	744	101.5	419.5	169.1	5.8	0	10	Cancer of the stomach

From every point of view, we may conclude that the pancreatic secretion is not necessarily disturbed by disturbed gastric secretion. It is rather increased in some cases.

COMMENT

We feel warranted in concluding that the pancreatic and biliary secretion is not disturbed as the consequence of disturbed gastric secretion. The foregoing observations suggest that the presence of hydrochloric acid is not necessary in order to stimulate normal pancreatic

TABLE 2.—*Results in Three Hour Specimens of Duodenal Contents*

Trypsin		
Below 30 kilo-units	1 case	
From 30 to 120 kilo-units	9 cases	
More than 120 kilo-units	2 cases	
Average of the whole (17 examinations)		99.9 kilo-units
Average of the cases showing more than 30 kilo-units		108.1 kilo-units
Amylase		
Below 50 kilo-units	1 case	
From 50 to 300 kilo-units	10 cases	
More than 300 kilo-units	1 case	
Average of the whole		272.5 kilo-units
Average of the cases showing more than 50 kilo-units		296.9 kilo-units
Lipase		
Below 50 kilo-units	2 cases	
From 50 to 300 kilo-units	8 cases	
More than 300 kilo-units	2 cases	
Average of the whole		161.3 kilo-units
Average of the cases showing more than 50 kilo-units		191.2 kilo-units
Bile Pigment		
Below 5 mg.	1 case	
More than 5 mg.	11 cases	
Average of the whole		21.4 mg.
Average of the cases showing more than 5 mg.		25.1 mg.

TABLE 3.—*Data of Enzymatic Activity*

Trypsin	
Below 500 kilo-units	1 case
More than 500 kilo-units	11 cases
Amylase	
Below 600 kilo-units	0
More than 600 kilo-units	12 cases
Lipase	
Below 600 kilo-units	2 cases
More than 600 kilo-units	10 cases

secretory activity. We had had much experience in normal cases, showing that a profuse secretion of pancreatic juice occurred during fasting when the gastric content drawn simultaneously with the pancreatic juice by means of the gastric tube did not show an acid reaction. The secretin mechanism is generally accepted and no doubt plays a rôle in normal digestion; however, we are of the opinion that this mechanism has been overemphasized. The facts that secretin is detected in nearly the same concentration in two thirds of the small intestine and that the acid chyme soon becomes alkaline on entering the intestinal tract show that only a small part of this hormone

partakes in this mechanism. It is highly suggestive that some energetic and important mechanism, other than the secretin mechanism, exists for promoting the pancreatic secretion. The evidence of this mechanism will be suggested in the fourth paper of this series.

CONCLUSIONS

The enzymatic activity of the duodenal return during three hours' collection was estimated. Evidence that the pancreatic secretion was disturbed as the consequence of disturbed gastric secretion was not found. On the contrary, there were cases in which an increased activity was detected, so that the general average of tryptic, amylolytic and lipolytic efficiency was much higher in comparison with that of normal gastric secretion. If one takes the highest value of hourly or half hourly specimens, the enzymatic activity was usually over the minimal normal limit. From these observations, it is evident that the presence of hydrochloric acid is not necessary in order to stimulate normal pancreatic secretory activity. The importance of the secretin mechanism seems to have been overemphasized. It is highly suggestive that some powerful stimulating mechanism other than that of secretin exists.

COARCTATION OF THE AORTA

A CASE OF THE ADULT TYPE IN A CHILD SIX MONTHS OF AGE *

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Coarctation is the term applied to the congenital stricture of the arch of the aorta below the origin of the left subclavian artery. This condition exists in two distinct forms as differentiated by Bonnet:[1] the "infantile" and "adult" types, according to the morphology and, possibly, the etiology of the lesion. In the first group he places cases presenting a diffuse narrowing of the fetal isthmus of the aorta, which may be regarded as the persistence of the normal relationship before closure of the ductus arteriosus. In the "adult" type there is found a relatively abrupt stricture, even complete obliteration, at or in the immediate vicinity of the ligamentum arteriosum. The constriction often resembles that produced by a ligature around a vessel and has been (probably erroneously) termed nondevelopmental and attributed to postpartum extension of the tissue of the ductus into the wall of the aorta. This explanation was first advanced by Craigie [2] and has been known as the skodaic theory. As late as July, 1927, this theory was mentioned by Mackenzie,[3] in spite of its inapplicability in cases in which stricture coexists with more or less patency of the ductus itself, and in cases in which a membranous ridge is present at the inner aspect of the stricture. The more probable explanation was advanced earlier by Reynaud,[4] Rokitansky [5] and Loriga,[6] and emphasized by Hamilton and Abbott [7] in a recent paper, as being due to "a true abnormality of development arising in embryonic life in the descending limb of the

* Submitted for publication, Dec. 12, 1928.

* From the Pathological Laboratory of Harlem Hospital.

1. Bonnet, L. M.: Sur la lésion dite sténose congénitale de l'aorte, Rev. de méd. 1903, vol. 23.

2. Craigie, D.: Instance of Obliteration of the Aorta Beyond the Arch, Edinburgh M. J. **56:** 427, 1841.

3. Mackenzie, G. M.: Coarctation of the Aorta, Am. J. M. Sc. **174:** 87, 1927.

4. Reynaud, A.: Observation d'une obliteration presque complete de l'aorte, Jour. hebd. de méd. **1:** 161, 1828.

5. Rokitansky-Dlouhy: Handbuch der speciellen pathologischen Anatomie, ed. 3, 1856, p. 337.

6. Loriga, G.: Stenosi ed obliterazione congenita dell'aorta, Riv. clin. di Bologna **7:** 529, 1887.

7. Hamilton, W. F., and Abbott, M. E.: Coarctation of the Aorta of Adult Type, Am. Heart J. **3:** 381, 1928.

primitive left aorta at the point of junction of the fourth, fifth and sixth arches of this side." In some measure of support of the latter theory, two cases of the "adult" type of coarctation, present shortly after birth, are mentioned by them, the first from Ettlinger [8] in an infant 17 days old, and the second from Wadstein [9] in an infant, aged 7 months. The case we are reporting in this paper is another of the "adult" type of coarctation in a child, aged 6 months.

REPORT OF CASE

History.—P. E., a boy, aged 6 months, born in the United States of Porto Rican parents, was admitted to the Harlem Hospital on July 26, 1928. The child left the Willard Parker Hospital eighteen days before, after having been under treatment there for diphtheria for the preceding two weeks. A cough was noticed at the time he arrived home, the expectorated sputum being white and thick resembling curdled milk. Two days before admission to our hospital, the child became extremely ill and was brought to the pediatric clinic, where treatment was prescribed, and he was sent home. On the day before admission he refused to suckle, but since then he has taken a little nourishment by spoon. His temperature had been high for the two days previous to admission. He cried little, but his voice became weaker.

He was born at the Lying-In Hospital in New York, on Jan. 24, 1928, at full term, delivery being spontaneous. He was breast fed up to the time he was taken to the Willard Parker Hospital and again after his return home. He was an only child, the mother never having been pregnant before. The mother and father were living and well.

Physical Examination.—The patient, a colored male infant, 6 months of age, was lying in bed in a comatose condition. He had a rapid respiration, rapid, thready pulse and a high temperature. He was obviously acutely ill. The head was normal in size and shape; the posterior fontanel was closed, and the anterior fontanel admitted the tip of a little finger. There were no craniotabes. The sclerae were clear, and the pupils pinpoint in size and fixed to light. There was incoordination of the extrinsic eye muscles. The ears and nose were normal. The anterior pillars of the fauces were slightly injected, and the lips were cyanotic. The neck flexed normally, and there were no abnormal pulsations or thrills. The chest was normal in shape, except for Hutchinson's grooves. The lungs were clear on percussion, but were full of loud subcrepitant râles heard both anteriorly and posteriorly. Patches of marked bronchial breathing with increased voice sounds were present. The heart sounds were obscured by the pulmonary signs. The breathing was mostly abdominal. There was moderate distention, but masses, tenderness and rigidity were not observed. The extremities were normal. There were no marked epiphyseal enlargements. The reflexes were normal.

The patient's temperature on admission was 105.2 F., the pulse rate 90 and the respiratory rate 50. The child died a few hours later. Cultures of the blood and spinal fluid taken immediately after death, under sterile conditions, were negative after four days.

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8. Ettlinger: Zur Casuistik der angeborenen Herzfehler, Klin. Wchnschr. **19**: 399, 1882.

9. Wadstein, E.: Stenos och obliteration af aorta vid eller i närheten af ductus botalli, Lund, 1897.

Autopsy.—The body was that of a colored male child about 6 months of age. It was fairly well developed but somewhat emaciated. Rigor mortis was complete sixteen hours post mortem. There were no signs of jaundice, edema or petechiae. The tonsils, thyroid and thymus were normal.

The chest was symmetrical. The pleural cavities did not contain any free fluid, and the pleura was smooth but dulled in appearance. The lungs were firm and airless practically throughout, with exception of the right middle lobe. On section, the lung tissue was a mottled dark red and gray, irregularly raised and granular in appearance. The blood vessels were normal. The left bronchus 1 cm. from its bifurcation presented an area of necrosis on its walls, 4 mm. in diameter. On opening this bronchus longitudinal fissures appeared in the necrotic area. A probe passed into these small artificial fissures pointed to the region of the ductus botalli. The connective tissue lying between the necrotic portion of the trachea and this same region was thickened and injected but did not contain any free pus. There was an abrupt marked stricture of the aorta directly at the point where it was joined by the obliterated ductus. The aorta was dilated slightly above and below the stricture. The circumference of the aorta at the aortic valve was 3.2 cm.; at the widest part of the ascending portion, 3.1 cm.; at the widest part of the arch, 3 cm.; at the widest part just above the coarctation, 2.9 cm.; at the coarctation, 0.66 cm., and at the widest part just below the coarctation, 2.9 cm.

The heart was enlarged, the pericardium was smooth and did not contain any excess fluid. The cardiac enlargement was due to moderate hypertrophy of the left ventricle. The valves were normal. The foramen ovale was patent. There was no increase in the size of the superior thoracic vessels, nor were other vascular anomalies present. The abdominal organs presented only congestion. The gastro-intestinal and genito-urinary tracts were normal.

The diagnosis was bilateral confluent bronchopneumonia, coarctation of the aorta, localized necrosis of the left bronchus, and congestion of the abdominal organs.

COMMENT

The symptoms of coarctation when present are: (1) dyspnea, usually not so marked as in other forms of congenital heart disease; (2) results of an unequal circulation with unequal pressure, such as headache and coldness of the lower extremities. Among the signs may be cyanosis, a loud precordial murmur, unequal pulse rates, weakness of the dorsalis pedis and visible pulsation in the upper part of the thoracic region. The x-ray picture may show an absence of the aortic bulge in the second left interspace. Other congenital cardiac lesions may accompany this abnormality. According to the severity of the lesion, a case will fall into one of the three following groups, as indicated by Hamilton and Abbott: (a) cases in which the condition is apparently entirely latent; (b) cases occurring in previously robust and vigorous persons, in the full tide of early adult life, in whom signs of cardiac insufficiency may suddenly set in as the result of what would otherwise be an inadequate cause; (c) a few cases in which signs of vascular or cardiac disability exist from early childhood.

It is difficult to state what part the anomaly played in the sequence of events leading to this child's death, since bronchopneumonia follow-

ing an acute infectious disease is a common enough cause of death in children. We may feel, however, that because of the absence of symptoms of cardiac disease before the initial illness and in view of the marked stenosis existing, this case probably fits into group b, although it is likely that had the child lived to an older age it would have fitted into group c.

It is interesting to note that cases of the "adult" type of coarctation usually present only minor anomalies of the cardiovascular system. This is just the opposite of what is found in the "infantile" type. In our case the sole accompanying anomaly was a patent foramen ovale. There occurred, however, two of the three important secondary changes, though to only a mild degree: first, the moderate dilatation above and below the stricture, and second, the moderate hypertrophy of the left side of the heart. The development of a collateral circulation, the most striking of the secondary features, was entirely absent. In view of the degree of the stricture this may again be attributed to the age of the patient.

A further point of interest in the case is the significant position of the focal necrosis of the left branch of the bronchus in relation to the coarctation and the ligamentum arteriosum. It seems reasonable that the pressure of the blood stream through the narrowed lumen exerted sufficient traction on the ligamentum and the tissue surrounding it to have caused mechanical irritation of the adjacent bronchus and so provided a reason for the greater involvement of the bronchus at this point during the recent illness. The mechanism would be similar to that described in the production of traction diverticula of the esophagus. As a matter of fact, the traction of the ligamentum arteriosum, said by some to be one of the causes of coarctation, is believed to be the cause of the conical aneurysms produced in the wall of the aorta at this point.

SUMMARY

1. Coarctation of the aorta may be either "infantile" or "adult." The first term is applied to those cases presenting a diffuse narrowing of the fetal isthmus; the second, to those presenting a relatively abrupt stricture, varying in degree, in the vicinity of the ligamentum arteriosum.

2. A child, 6 months old, who was admitted with a bronchopneumonia of at least two days' duration, died some hours after admission. The developmental and family history was negative, but the infant had been ill with diphtheria and discharged from the hospital as cured eighteen days previous to admission. No cardiac signs were elicited on examination because of the masking signs of bronchopneumonia.

3. Autopsy revealed, in addition to an extensive bronchopneumonia, a localized necrosis of the left bronchus and a coarctation of the aorta

of the "adult" type. This was accompanied by a patent foramen ovale, a moderate dilatation above and below the stricture and a moderate hypertrophy of the left side of the heart.

CONCLUSIONS

1. The focal necrosis found in the bronchus was probably initiated by the pressure of the blood stream flowing through a narrowed lumen and exerting sufficient traction on the ligamentum at this point to have caused mechanical irritation of the adjacent bronchus during the patient's recent attack of diphtheria.

2. The minor degree of accompanying anomalies and the presence of two of the three important secondary cardiovascular changes are consistent with the adult type of coarctation.

3. This case is the third on record presenting the adult type of coarctation in an infant shortly after birth and therefore supporting the developmental theory of origin.

4. The "adult" type of coarctation frequently and erroneously has been termed nondevelopmental. It is a true abnormality of development arising in the descending limb of the primitive left aorta.

Book Reviews

LEHRBUCH DER BLUTKRANKHEITEN FÜR ÄRZTE UND STUDIERENDE. By PROF. DR. HANS HIRSCHFELD, Director of the Hematological Division of the University Institute for Cancer Research, Charité, Berlin, and Professor at the University of Berlin. Price, Rm. 22, bound Rm. 24. Pp. 263, with 48 illustrations. Leipzig: J. A. Barth, 1928.

This is not a handbook for the specialist in hematology whose main interest is in the cytology of the blood. It is, as the title indicates, a textbook of diseases of the blood, intended primarily for the clinician and the medical student. As in the first edition of this book, clinical features and therapeutics are emphasized, while the discussion of blood pictures is restricted to what can be easily understood by those who have not had special training in morphologic hematology.

In some instances, this plan to limit the discussion of the cytology of the blood has led to the omission of some features which are important for differential diagnosis; for example, the spherical shape of the microcytes in hereditary hemolytic jaundice, the peculiar and characteristic neutrophil leukocyte of pernicious anemia, the character of the lymphocytes in benign lymphadenosis (infectious mononucleosis) and lymphatic reactions compared with those of acute lymphatic leukemia.

The general part of the book contains a brief but useful account of the common technical methods employed for the microscopic examination of the blood, including a description and illustration of the Hirschfeld precision pipets for accurately measuring the blood column and diluting fluid for cell counts. There are brief sections on the physicochemical and biologic properties of the blood, including the technic for determining blood groups. A section follows on the formation and destruction of blood, with a brief description of the histology of the blood-forming organs. The dualistic view of Naegeli is accepted as expressing the relationships of blood cells, with latent myeloid tissue in the spleen, in the form of oxydase-positive cells of the pulp and as adventitial cells in lymph nodes and liver, providing the mechanism for myeloid metaplasia of these organs in various pathologic states.

The section on the general pathology of the blood is one of the most interesting parts of the book. The general principles which govern the alteration of the blood are discussed, and the proper background is developed for the part dealing with diseases of the blood and blood-forming organs. It includes a discussion of the "shift to the left" in the leukocyte formula and a useful table presenting a grouping of diseases and pathologic states according to the type of leukocytosis which accompanies them.

More than half of the book is devoted to diseases of the blood and blood-forming organs, 41 pages being given to the anemias. Among the hemolytic anemias are included only those that show hemoglobinemia, such as various symptomatic types (black water fever, snake venom, saponin, etc.) and paroxysmal hemoglobinemia. Pernicious anemia, hemolytic jaundice and others which are frequently classified with the hemolytic anemias are excluded, because the destruction of erythrocytes takes place outside the blood stream. The other diseases are discussed under the following headings: hemoblastoses of the leukoblastic system (leukemia, chloroma) and of the erythroblastic apparatus (erythremia), genuine tumors of the hematopoietic system (lymphosarcoma, multiple myeloma, etc.), infectious granulating lymphomatoses (tuberculous, syphilitic, Hodgkins), diseases of the spleen, hemorrhagic diatheses and protozoan diseases of the blood. These chapters are followed by sections on general therapy of diseases of the blood, and secondary changes in the blood in diseases which are not primarily those of the blood. Finally there are a number of tables giving typical pictures of the blood illustrating the diagnostic and differential diagnostic importance of morphologic examinations of the blood.

In general, the more important diseases of the blood are discussed under the following headings: general clinical features, course, prognosis, pathologic anatomy, pathogenesis, differential diagnosis and therapy. The arrangement of the subject matter is logical and convenient for ready reference. Only well established facts are presented. There is an almost complete omission of controversial material and discussion of the literature. In spite of these intentional omissions this revised edition, with its modern point of view, should meet the requirements of those who wish to use it in medical practice, but who do not care to specialize in diseases of the blood. The revision shows many additions in both text and illustrations corresponding to the rapid advance which has been made in this field.

LABORATORY DIAGNOSIS AND EXPERIMENTAL METHODS IN TUBERCULOSIS. HENRY STUART WILLIS, the Johns Hopkins University and Hospital, with a Chapter on Tuberculocomplement Fixation, by J. Stanley Wooley, Loomis Sanitarium. Price, cloth, $3.50; keratol, $4.25. Pp. 330, with illustrations and references. Springfield, Ill.: Charles C. Thomas, 1928.

In this book, according to the preface, an attempt is made to describe the more important methods of laboratory diagnosis of tuberculosis and to consider some of the more significant procedures and principles involved in the experimental study of the disease.

The organization of the book is strikingly good and makes the work an invaluable and most accessible aid to the laboratory worker. Part 1 deals with general considerations of the fluids and excreta of the body. In part 2 the various bacteriologic methods of diagnosis are concisely and clearly described. The following sections give the methods of diagnosis by tuberculin and by serologic methods. Lastly, there are descriptions of methods for producing and studying the disease in animals and discussions of the technic of tissue culture and histologic technic for handling tissues. At the end of the book there is even a list of the equipment needed for a tuberculosis laboratory, with prices.

Dr. Willis' keen insight into the difficult details confronting the unaccustomed laboratory worker especially is clearly evident from the careful description of technic. Although the book is intended rather as a description of methods than as a discussion of theories, there is a great deal of valuable and often inaccessible theoretical information. References to an extensive bibliography lead the research worker to original sources. Data concerning the disinfecting capacities of varying degrees of heat and various concentrations of chemicals on the tubercle bacillus are especially commendable. The descriptions of the vital staining technic for studying the blood and tissues, of tissue culture methods and of the histologic technic for handling tissues are also valuable.

Dr. Allen Krause gives the following good description of the manual in his introduction: "The book will have been worth while if it succeeds in teaching that the laboratory diagnosis of the ordinary cases of tuberculosis can be accomplished by simple methods in an ordinary physician's hands in an ordinary physician's office."

CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF HEART DISEASE. JOSEPH H. BAINTON, M.D., W. C. MUNLY, M.D., M.C., U.S.A., ROBERT L. LEVY, M.D., and HAROLD E. B. PARDEE, M.D. (Chairman), a Committee Appointed by the Heart Committee of the New York Tuberculosis and Health Association. Arranged in conformity with the nomenclature for cardiac diagnosis approved by the American Heart Association. Price, $1.50. Pp. 92. New York: Paul B. Hoeber, 1928.

The effective study of a chronic disease such as heart disease necessitates the accumulation of clinical data in many places over long periods of time. This cannot be accomplished satisfactorily unless a uniform nomenclature is adopted

by the clinics encouraging such a study. The importance of precise labeling should be self-evident, and precision and uniformity in labeling depend on the accurate understanding of the labels.

This little book defines with remarkable clarity the criteria for the diagnosis and classification of pathologic conditions of the heart. The diagnostic nomenclature is that adopted by the American Heart Association. It was originally prepared and adopted by the Committee on Cardiac Clinics of the New York Heart Association and was introduced, in 1923, into the various clinics of that organization which is now the Heart Committee of the New York Tuberculosis and Health Association. In the opinion of the reviewer it should prove satisfactory in any clinic.

The major portion of the book is devoted to a discussion of the criteria for cardiac diagnosis. The belief is expressed that a comprehensive diagnosis should consist of four parts: etiologic, anatomic, physiologic and functional; that is to say, it should not only describe the structural changes in the heart but give the causes of such changes, indicating the type of disturbance of physiologic function, and defining the functional capacity of the heart. The descriptions and definitions are given concisely and clearly.

The committee has done a genuine service to the medical profession in the publication of this valuable book.

THE OPIUM PROBLEM. CHARLES E. TERRY and MILDRED PELLENS. For the Committee on Drug Addictions in Collaboration with the Bureau of Social Hygiene. Cloth. Gratis. Pp. 1,042, with illustrations. New York: Committee on Drug Addictions, 1928.

This work is unique in its composition. It is a literary production in that it presents the problem of opium in its historic, physiologic, pathologic and forensic phases, purely from the standpoint of citation. The authors have quoted or summarized the essential features of approximately 400 references, consequently making this essentially a source book. In general, they have refrained from presenting their own conclusions; instead, they present the interpretations of the problem made by the different writers. This work is valuable to the student of almost any phase of the morphine problem, whether from the strictly scientific or the legal standpoint.

THE DUODENUM: MEDICAL, RADIOLOGIC AND SURGICAL STUDIES. PIERRE DUVAL, JEAN CHARLES RAUX and HENRI BECLERE, Surgical Clinic, Faculty of Medicine, Paris. Translated by E. P. Quain, M.D. Price, $5. Pp. 205. St. Louis: C. V. Mosby Company, 1928.

The first half of this monograph is devoted to a discussion of the etiology, symptoms, diagnosis and treatment of periduodenitis. Beginning with cases of disease of the gallbladder in which the duodenum is involved by contiguity, the authors proceed to differentiate the symptoms due to disease of the gallbladder *per se* and those due to periduodenitis *per se*. The evidence submitted is entirely inadequate to justify the conclusions drawn. The same criticism applies to the chapter on essential and stenosing periduodenitis. Taken as a whole, facts submitted, including those of serial roentgenograms and operative controls, do not justify the attitude taken.

The chapter on chronic compression of the third portion of the duodenum seems a little more reasonable. Here, too, the authors seem unable to keep their enthusiasm under control. It is difficult for one who is unversed in "right-sided constipation and cecocolonic stercoral stasis" to conceive of a colonic type of duodenal stenosis.

The chapter on the radiologic signs of ulcer of the duodenal bulb is a well written, concrete presentation of fact. It is the really good part of the book. There is a similarly concrete discussion of intoxication in experimental intestinal obstruction. The clinical application of this condition in incomplete duodenal stenosis is not so obvious as it seems to have been to the authors.

CLINICAL MEDICINE. OSCAR W. RETHEA, M.D., PH.G., Professor of Therapeutics, Tulane Graduate School of Medicine, and Professor of Clinical Therapeutics, Tulane School of Medicine. Cloth. Price, $7.50. Pp. 700. Philadelphia: W. B. Saunders Company, 1928.

In the preface the author states that he has endeavored constantly to keep in mind that the great majority of patients must be treated in homes and under conditions which offer limited aid to the physician. The book concerns chiefly the diagnosis and treatment of about 100 of the most common diseases coming within the province of internal medicine. It is what it claims to be: a practical discussion of ordinary diagnosis and treatment, in which etiology and pathology receive little consideration. It will probably be welcomed by many practitioners.

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